

INVESTIGATION OF GEOMETRICAL ISOMERISM
AND TAUTOMERISM IN SOME NEW
BENZOTHIAZOLE -2- CARBOXAMIDINES

THESE

présentée à la Faculté des sciences de l'Université de Genève
pour obtenir le grade de docteur ès sciences chimiques

par

Dinesh Pandurang RAO

de

l'Inde

Thèse No 1680

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La Faculté des sciences, sur le préavis du professeur ordinaire Th. Posternak, directeur de thèse et d'une commission composée du professeur ordinaire K. Schaffner et du docteur P. Baudet, autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

Genève, le 27 septembre 1974

Le doyen :
Jean Muller

Thèse No 1680



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Finally, to my wife, Renée, who critically read the manuscript and made many valuable suggestions, I wish to express my gratitude.

TO MY PARENTS

RESUME

Ce travail avait pour objet la préparation et l'étude de systèmes triadiques dans le cas particulier des benzothiazole-2-carboxamidines obtenues par condensation du benzothiazole-2-carbonitrile avec des amines primaires. Une série de benzothiazole-2-carboxamidines N-monosubstituées a donc été préparée.

La condensation du benzothiazole-2-carboximate avec des esters d'acides α -aminés conduit à l'obtention d'amidines correspondant à l'une seule des formes tautomères théoriquement possibles, pour laquelle les isomères syn- et anti- relatifs au groupement imino ont pu être isolés et caractérisés par leurs spectres ir, uv et rmn. Les esters carboxyliques et les acides libres des isomères syn- se présentent exclusivement sous la forme énolique tandis que la forme la plus stable des isomères anti- semble être celle qui conserve le groupement carbonyle intact.

Lorsque la condensation a été effectuée à partir d'esters d'acides α -aminés optiquement actifs les dérivés anti- se sont formés avec rétention de la configuration alors que les dérivés syn- obtenus étaient optiquement inactifs en raison même de leur structure énolisée.

L'attribution des structures respectives a été confirmée par la formation de dérivés cycliques dans les deux cas.

a) Cyclisation thermique :

Chauffés, les isomères syn- aussi bien qu'anti- donnent un dérivé cyclique, le même. Dans le processus de cyclisation des isomères anti- l'existence d'un intermédiaire dont il a été possible de faire la synthèse, a été mise en évidence.

b) Isomérisation par catalyse acide :

L'action de l'acide bromhydrique sur des amidines anti-(NH₂) (avec un substituant t-butyl ester) (isomère E) optiquement actives a conduit à la formation de dérivés syn- (isomères Z) énoisés, dénués de pouvoir rotatoire. Ceci est une conséquence de la structure plane de la molécule énoisée. La possibilité d'isoler de tels composés constitue un argument supplémentaire en faveur de l'existence d'intermédiaires plans dans le mécanisme de racémisation de molécules présentant le phénomène de tautométrie. Il y a formation d'acides α -aminés racémiques par hydrolyse acide des dérivés syn- .

Des amidinoacides sous forme imino ont pu être préparés à partir du benzothiazole-2-carboximide et du sel de lithium d'acides α -aminés. Par chauffage ces composés donnent les 4(5H)-imidazolones correspondantes, identiques à celles obtenues dans le cas des isomères syn- et anti- .

L'étude par spectroscopie ir a montré la prépondérance de la forme amino dans l'équilibre qui s'établit dans les solutions de ces dérivés N-monosubstitués des benzothiazole-2-carboxamidines.

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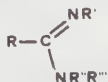
INTRODUCTION

Time has not invalidated the assumption of Hantzsch and Werner who, as early as 1890, predicted the existence of isomers in the case of oximes, pointing out an analogy between the carbon-carbon and the carbon-nitrogen double bonds. Today the knowledge of the tetrahedral nature of the nitrogen atom, along with the possibility of isolation of geometrical isomers around carbon-nitrogen double bond has even reinforced the value of their assumption.

The syn-anti (or cis-trans) isomers were then observed but only when an electronegative atom like oxygen, nitrogen, sulphur or halogen was bonded to the imino nitrogen. And the first successful attempt which firmly established the existence of such isomers in which carbon atom is bonded to imino nitrogen, was the isolation of geometric isomers of imines by Curtin (1).

The geometrical isomerism (2) in the case of aldimines (3-11), ketimines (12-19), oximes and oxime ethers (20-30, 95), hydrazones and azines (96-104), N-halimines (105-109), imidates, iminocarbonates and related compounds (110-117) have been reported in the literature.

Amidine is one of the triadic systems containing carbon-nitrogen double bond commonly encountered in organic and biological molecules. They are mono-acid bases characterized by the structural grouping :



and may be classified into five general types depending on the number and the distribution of the substituents on the nitrogen atoms.

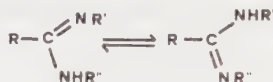
a) Unsubstituted



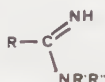
b) Monosubstituted



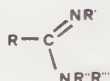
c) N,N'-disubstituted



d) N-disubstituted



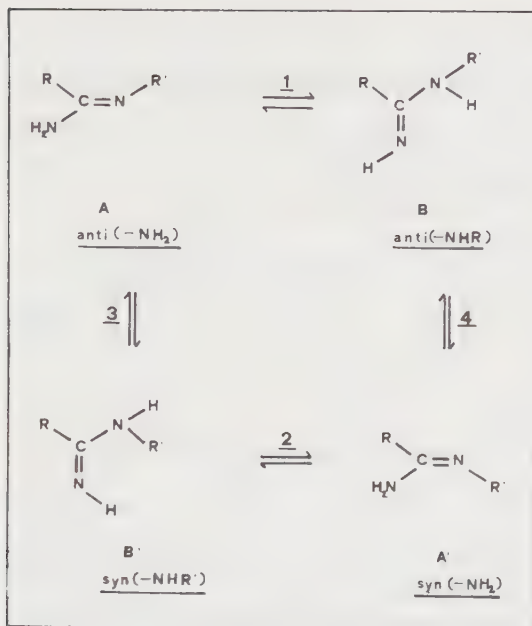
e) Trisubstituted



One hopes that mono- and N,N'-disubstituted amidines having different groups on the nitrogen atom would exhibit tautomerism. Although there is a considerable amount of experimental evidence supporting this assumption, no proof for the existence of the two tautomeric forms have been presented as yet (118). Numerous attempts have been made to isolate the two tautomeric forms, but they apparently all failed (64, 66, 119-121).

Experimental findings favouring the possibility of tautomerism are: 1) a single amidine results from a reaction designed to prepare two isomeric forms; 2) the alkylation of an amidine yields two products; 3) the hydrolysis of N,N'-disubstituted amidines produces a mixture of amides and amines (32).

The tautomeric equilibrium in amidine may be represented by the following equations¹.



Equations 1

In the above equations 1, 1, 2, 3, and 4 are each tautomeric pair of an amidine, involving an equilibrium between

1. amino form of amidine $\rightleftharpoons$ imino form of amidine

A

B

2. imino form of amidine $\rightleftharpoons$ amino form of amidine

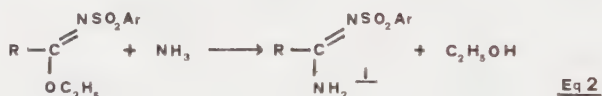
B'

A'

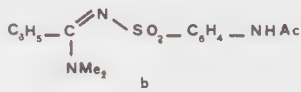
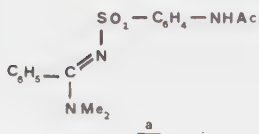
Now if by any means such as altering the experimental conditions or using a stabilizing substituent, it may be possible to displace both the equilibriums 1 and 2 in favour of the amino form, then it would be possible to isolate the two geometrical isomers A and A'.

Looking into the reported work on the tautomerism and geometrical isomerism may clarify some of the points.

Barber (122) was able to isolate the two forms of a substituted sulphonamidine (an amidine substituted with a highly electronegative group). He isolated the two tautomers I and II as shown in the equations 2 and 3:

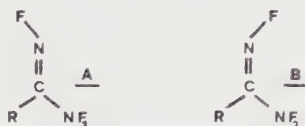


Form I could easily be converted into the stable form II. Barber established the above structures on the basis of their hydrolytic products. Angyal and Warburton (123) repeated the preparation of the two forms of arylsulphonylbenzamidines described by Barber and from their ultraviolet absorption spectra concluded that the structure proposed by Barber for these compounds should be reversed. They also obtained two isomers of N-(4-acetamidophenyl-sulphonyl)-N,N'-dimethyl benzamidine and they deduced that these were the geometrical isomers (see a and b below)



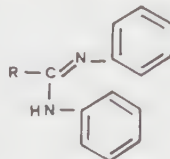
In a recent work on the sulphonyl-benzamidines and guanidines, Tinkler (124) on the basis of solution infrared spectra of these compounds proposed the predominance of the imino tautomer over the amino tautomer. While Danilewicz, Sewell and Thurman (125) have claimed that the isolation of tautomers and geometrical isomers of arylsulphonyl amidines have been shown to be incorrect. Chemical and spectroscopic evidence in particular that from ^1H n.m.r. spectrum of N-(3-chlorophenylsulphonyl)(N'-N¹⁵) acetamide has shown this compound to exist predominantly in the amino form.

Ross, Coon and Hill (126) were able to separate the geometrical isomers of N,N,N'-trifluoroalkyl amidines and on the basis of ^{19}F n.m.r. analysis and volatility observed in distillations which agreed with the relative retention times on glpc. More volatile A (see below) was assigned anti- while the less volatile B was assigned syn- . The n.m.r. investigation of these two isomers



gave identical proton spectra with the same splitting and chemical shifts. But the ^{19}F spectra differ in that , the NF_2 peak ($\psi^* -47.0$) of isomer A was downfield from the NF_2 peak ($\psi^* -43.7$) of isomer B. Conversely the $\text{C}=\text{NF}$ peak ($\psi^* -11.3$) of isomer A was upfield from $\text{C}=\text{NF}$ peak ($\psi^* -16.2$) of isomer B.

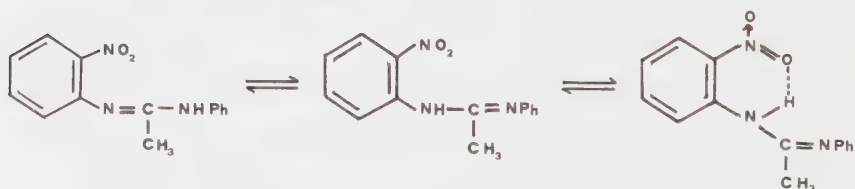
Shigorin and Syrkin (127-128) have studied Raman spectra of the amidines of the type:



in chloroformic solution and have shown they contain always two bands situated between 1636 and 1658 cm^{-1} . According to these authors these two bands arise from the mixture of syn- and anti-isomers in each of the six different substituted amidines examined by them.

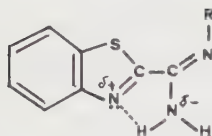
Recently, Heesing and Maleck (129) have studied isomerism and tautomerism in N-haloguanidines and amidines. The n.m.r. spectra of these compounds show NH-CH coupling particularly that of the C-H bands. In the light of the weak basicity of these compounds, the rate of interchange was slow and it was possible to clarify precisely the isomerism and tautomerism.

Runner, Kilpatrick and Wagner (130) have examined polarographically the three isomeric N-phenyl-N'-nitrophenyl acetamidines and have discussed tautomerism of amidines containing a mobile hydrogen and considered the possibility that influences might be brought to bear the stabilization of a given tautomer. These authors have selected the compounds wherein an internal hydrogen bonding may result into a restricted prototropy. (Eq 4)

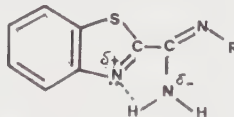


Eq 4

In the present work we have been able to isolate the two geometrical isomers C : anti-(NH₂) and C' : syn-(NH₂) of N-monosubstituted 2-benzothiazolecarboxamidines, (54).



C
anti-(NH₂)

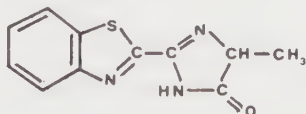


C'
syn-(NH₂)

These amidines display a hydrogen bonding in which one H of the amino function is linked to the heterocyclic nitrogen. The resulting tricyclic planar system should be of lower energy and we could expect further stabilization by resonance in this heterocyclic conjugated system.

It has been possible to synthesize two series of the isomers C and C' each of them leading to the same 5-membered heterocycle by thermic transformation.

The work started as it was of our interest to synthesize a compound of the type:



The desired product was obtained by the reaction between benzothiazole-2-carbonitrile and alanine ethyl ester in methanol. To have more understanding about this reaction we made another synthesis using phenylalanine ethyl ester under the same conditions.

To our surprise the analytical data showed that we got just an addition product between the two reactants. In the infrared spectrum the expected ester absorption was absent. After another experiment carried out with glycine ethylester (again under the same conditions) the infrared spectrum of the resulting product showed an ester carbonyl frequency and two NH stretching vibrations.

Thus the analytical data obtained led to suppose that we had one representative of each of the isomeric series.

These few points gave the impetus for the following work.

PREPARATION OF AMIDINES

The preparation and reaction of iminoesters were studied many years ago by Pinner (31) who referred to them as 'Imidoäther' (Iminoether). More recent reviews have proposed the name 'Imidates or Imidoates' to these compounds, as they are esters of the hypothetical imidic acids, $RC(=NH)OH$ (32,33).

The Pinner synthesis consists in condensing a nitrile and an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide (31).(Eq 5)



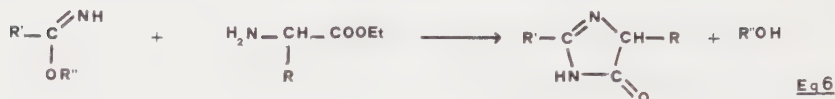
Variations of this method have since appeared and alternative methods for the preparation of imidates are available, (33). But Pinner's synthesis is still the one commonly employed in the preparation of these weak bases.

Amidines can be prepared by any of several general methods but many of them have been synthesized by the reaction between imidates and amines (32). Important information about their physical and chemical properties is available (32). Amidines are mono-acid bases. They are stronger bases than typical amines but are not as strong as bases as guanidines.

Monosubstituted amidines have been prepared by the reaction of imidates with amines under particular reaction conditions. Instead of simple amidines, cyclic amidines can be prepared by introducing other reactive substituents into the amines or by varying the reaction conditions.

Thus Finger (34,35) reported the formation of 5(4)-imidazolone when the reactants, iminoesters and α -amino acid esters in molecular proportions, were brought into contact at room

temperature with or without ether as a diluent (Eq6).



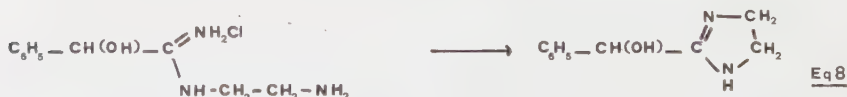
The method is applicable to the preparation of a great variety of imidazolones since R, R' may be aromatic or aliphatic in nature(42,43).

While Tietz and Petersen (36-38) and W. Ried et al (39,40,44) prepared monosubstituted amidino acids by the reaction of an imidate with an α -amino acid. Optically active amidino acids have been prepared from optically active α -amino acids (39). The same authors on the basis of infrared spectra have proposed a zwitterionic structure to these amidino acids. (Eq7).



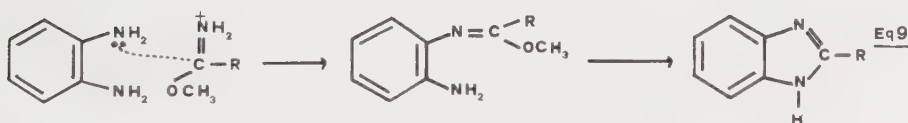
Amino nitriles (45) and amino amides (41,46) have been reacted with simple imidates to give N-monosubstituted amidines and then to give imidazole derivatives.

Bristow (47) was able to isolate and characterize the intermediate N-(2-aminoethyl)mandelamidine hydrochloride which lost ammonia slowly at room temperature (more readily in hot alcohol) to give the corresponding 2-imidazoline (Eq8).



2-Imidazolines have been prepared extensively by heating 1,2-dialkylamines with imidates or their salts (48-50, 69-71).

King and Acheson (72) reinvestigated the preparation of benzimidazole (73) from imidates and o-phenylenediamine (74) and found that the presence of one or two equivalents of acid was necessary for the reaction to take place. They proposed that the mechanism of the reaction proceeded by attack of an imidate cation on the lone pair of electrons of one of the amino groups, with subsequent formation of the N-substituted imidate which by elimination of alcohol, cyclized through intramolecular condensation to give benzimidazole. (Eq 9)



SYNTHESIS OF ISOMERIC AMIDINES

ANTI (NH₂) - AMIDINES AND SYN (NH₂) -(OH) (OR) - AMIDINES .

The anti-(NH₂) amidines (E Isomers) were prepared by the reaction between an α -amino acid ester and benzothiazole-2-carboximide(or its hydrochloride)in ether(or methanol-ether mixture)as the solvent at room temperature. It was also possible to synthesize the isomeric amidines by starting with benzothiazole-2-carbonitrile and an α -amino acid ethyl ester in methanol at reflux, whereby syn(NH₂)-(OH) (OR) amidines (Z Isomers) were obtained. But when t-butyl esters of α -amino acids were used in the same conditions than ethyl esters, only the anti-(NH₂) amidines (E Isomers) were isolable, indicating the instability of sterically hindered t-butyl ester group in the syn-configuration.

It is quite possible that the two syn- and anti-isomers referred above can arise from the same intermediate I (see fig. 1) depending on the given reaction energy.

Thus the intermediate I (equation 10) can result from T₁ transition state characteristic of the nucleophilic addition (B_{Ac}², (75)) of primary amino group on the imino ester, which can give rise to anti-(NH₂) isomer at ambient temperature after T₂ transition state.

While in the boiling methanol, the intermediate I can be transformed by the transition state T₂' (see fig.2; equation 11) into a new intermediate I' which can be formulated as syn (NH₂)-carboxylic acid ester derivative. The intermediate I' should be sterically unstable, wherein the acidity of the α -carbon atom and the state of the molecule should play a pronounced role.

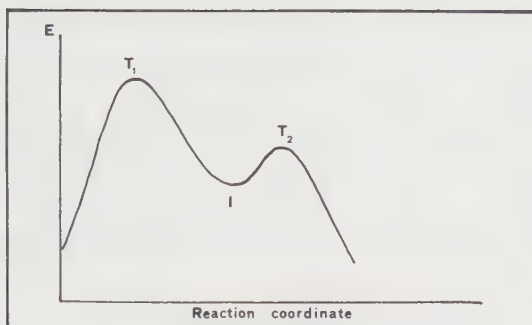
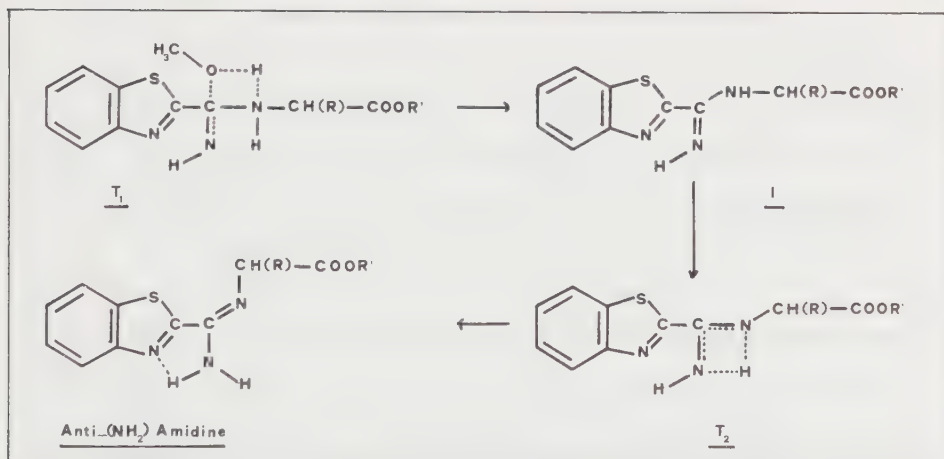


Fig 1 : Energy curve for a reaction with
an intermediate (case of anti-(NH₂)
amidine)



EQUATION 10

Thus a prototropic transformation induces a conjugative stabilization and at the same time the neutralization of the enolic form of the carboxylic acid ester (i.e. the formation of an internal salt) helps the formulation of syn(NH₂)-(OH)(OR) amidine (Z Isomer) containing an enolized carboxylic acid ester. Hence, this intermediate I' through T₃ transition state can give the enolic syn(NH₂)-(OH)(OR) amidine derivative (Z Isomer).

In short the aforesaid reaction pathway can be summarized by the following points :

- a) the formation of carbon-carbon double bond
- b) the enolization of carboxylic acid ester and
- c) the enlargement of N-CH-COOR angle

resulting in a decrease of the energy of this Z isomer, which arises from the effect of resonance and also from the formation of the sterically less hindered structure (a conjugated one). Besides the neutralization of the enolic OH of the ester function with that of the NH₂ group of the amidine function is another stabilizing factor which can be propounded.

The intermediate I gives rise to optically active anti-(NH₂) amidine (E Isomer), which indicates that the α-carbon atom of the imino acetic group (=N-CH(R)-COOR') of this intermediate remains in the Sp³ hybridization state through the T₂ transition state, according to the hypothetical reaction energy diagramme. Whereas optical inactivity of the syn(NH₂)-(OH)(OR) amidines (Z isomers) can be explained on the basis of the changes in the asymmetry of the α-carbon atom as it passes through the intermediate stage of I' and the last transition state of T₃. The tautomeric change and the formation of the resulting internal salt give the syn(NH₂)-(OH)(OR) amidine as an optically inactive product.

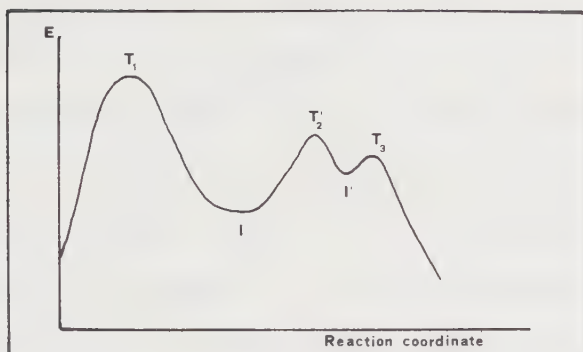
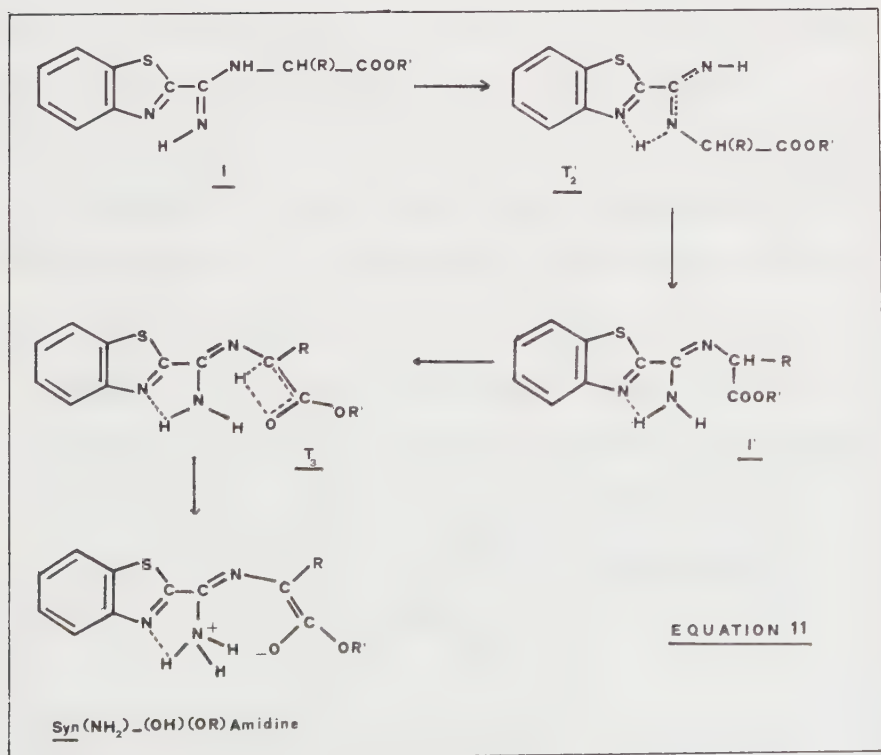


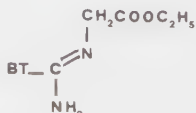
Fig 2 : Energy curve for a reaction with two intermediates (case of syn(NH₂)-(OH) (OR) amidine)



When the reaction between L-phenylalanine ethyl ester or L-alanine ethyl ester and benzothiazole-2-carboximidate was carried out in methanol as the solvent at room temperature, a yellow product (ca. 10% in the first and 5% in the second case respectively) was obtained. The ultraviolet spectra were not similar to those of the syn(NH₂)-(OH) (OH) amidines. This excludes the possibility of polymorphic forms. The infrared spectra showed absence of the carbonyl ester stretching frequency, while ν (NH) at 3250 cm⁻¹ and ν as(NH₃⁺) at 1538 cm⁻¹ infer an enolized and dipolar structure. But when the reaction was carried out with methanol-ether (ca. 1:5) mixture as a solvent at room temperature or at reflux in methanol, no presence of the described product could be detected.

The 2-benzothiazolecarboxamidines having α -amino acid ethyl ester substituent undergo facile tautomeric and isomeric transformations depending on the temperature or the reaction medium or the effect of the substituent on the α -carbon of the amino acid derivative. These transformations can even take place as a slow spontaneous process in the solid phase. But the amidines containing t-butyl ester functions were always in the anti-configuration, irrespective of any conditions used (refer: synthesis of /20/). The intermediate I' and the proposed transition states T₂ and T₃ are thus affected by the steric hindrance.

One exception to the above mentioned reaction sequence is the addition product between benzothiazole-2-carboximidate and glycine ethyl ester, which in spite of different reaction conditions, at reflux in methanol or at room temperature in methanol-ether mixture as a solvent, always gave anti-(NH₂) amidine (E Isomer) having the following structure :



ENOLIC AMIDINO ACID DERIVATIVES. $\text{SYN}(\text{NH}_2)-(\text{OH})(\text{OH})$ AMIDINES

(Z ISOMERS)

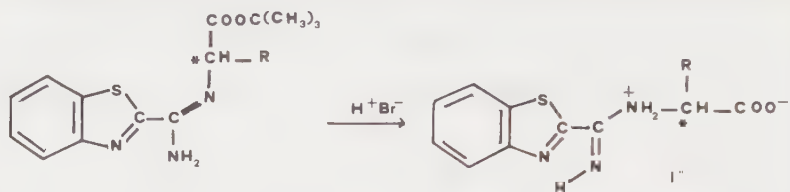
Isomerization of anti- (NH_2) t-butyl ester derivatives of Amidines.

Enolic amidino acid derivatives were synthesized in perfectly dry conditions by the action of hydrobromic acid (ca. 10 to 15%) in glacial acetic acid on optically active ester derivatives of anti- (NH_2) amidines. These amidines were isolated as syn- $(\text{NH}_2)-(\text{OH})(\text{OH})$ amidinium bromides (Z isomers). (Eq 12 A)

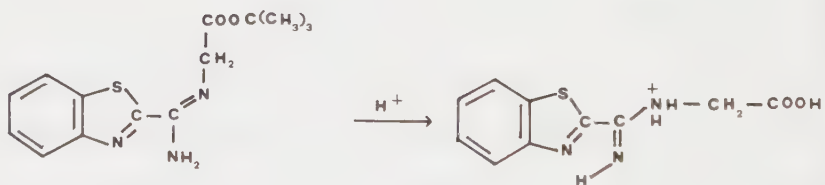
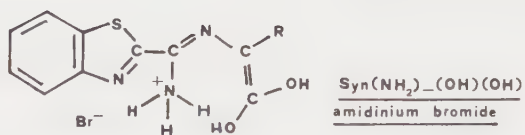
This reaction can be explained if we assume the formation of an intermediate I'' exhibiting the imino form of an amidine with a dipolar structure wherein the t-butyl ester group has been acidolysed to the corresponding carboxylic acid function. This intermediate could then evolve to the syn- $(\text{NH}_2)-(\text{OH})(\text{OH})$ amidine monohydrobromide derivative which will present no optical activity due to its planar (conjugated) structure.

Here also the glycine derivative of this amidino acid retains its normal carboxylic acid function, which is confirmed by its infra-red spectrum. Moreover on the basis of its ultraviolet spectrum it seemed that in dilute methanolic solution it exists in the imino form of amidine.

Thus we observed in the carboxylic acid or ethyl ester derivatives of 2-benzothiazolcarboxamidine a typical steric environment, viz., the absence of alkyl or other substituent does not favour the enolization of the carboxylic acid or ester function. The energy barrier at T_3 transition state should be higher and hence no isomerization may be possible (see equation 11 and equation 12 B)



A



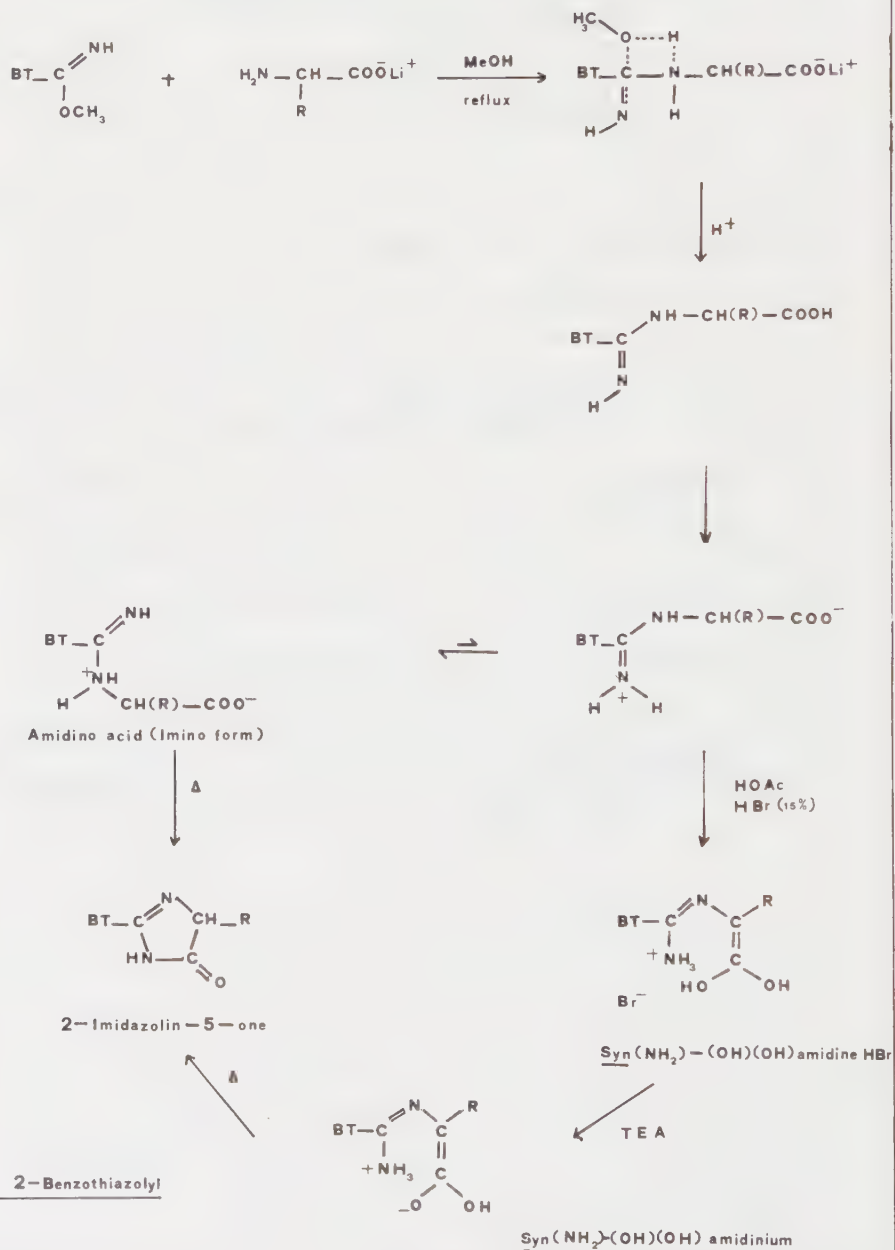
B

compd /61/

AMIDINO ACID DERIVATIVES. IMINO FORM OF AMIDINES.

(ZWITTERIONIC DERIVATIVES)

The reaction between benzothiazole-2-carboximide and the lithium salt of an α -amino acid in methanol at reflux gave an amidino acid (imino form) having a zwitterionic structure after neutralization with a mineral acid. (see equation 13). The structure of this amidino acid was confirmed by its infra red and ultra violet spectra. The possibility to isolate this compound establishes the proposed intermediates I and I'' (Fig 1, equation 10 and 12 resp) in the synthesis of anti(NH₂)amidines and the isomerization of anti(NH₂) t-butyl ester amidine derivatives into syn(NH₂)-(OH) (OH) amidinium bromide derivatives respectively. Independently syn(NH₂)-(OH) (OH) amidine derivatives can be prepared from this amidino acid (imino form) in the presence of HBr in glacial acetic acid. After neutralization of this amidinium bromide by TEA and sublimation the corresponding 2-imidazoline-5-one derivative has been obtained. Alternatively this cyclic derivative can be prepared by direct heating of the amidino acid (imino form) in high vacuum.



RESULTS AND DISCUSSION

Syn(NH₂)-(OH)(OC₂H₅) Amidines. (Z Isomers)

The study of syn(NH₂)-(OH)(OC₂H₅) amidines (Z isomers) is difficult as they slowly cyclise, even in the solid phase at room temperature into their corresponding 2-imidazolin-5-one derivatives. They are intensely yellow coloured compounds and were analysed immediately after their isolation. No melting points are reported for these compounds as the melting points observed were in fact those of their corresponding cyclic derivatives and are therefore mentioned in the paragraphs assigned to the preparation of these later products. (Refer /30/,/31/,/32/). In all, the successful synthesis of three different derivatives have been described. These compounds were obtained in a pure form. In other attempted cases, it was very difficult to isolate them in the pure form, as analysis showed always a little presence of the corresponding cyclic derivative. Acetylation of syn(NH₂)-(OH)(OC₂H₅) amidines in the presence of acetic anhydride in glacial acetic acid at room temperature gave 5-O-acetyl-2-imidazole derivatives, /37/,/38/.

The ultraviolet spectra of these isomers show two absorption maxima indicating a conjugated structure. Thus dilute methanolic solution of N-(1-benzyl-2-ethoxy-2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine,/7/, shows: λ max. 349 nm (ϵ 13250) and 227 nm (ϵ 19350), while N-(2-ethoxy-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarboxamidine,/8/, presents its maxima at λ max. 360 nm (ϵ 16150) and 225 nm (ϵ 12180), (see Fig 3). After about one week's time at room temperature the same respective solutions show the absorptions at λ max. 290 nm (ϵ 12140) and 227 nm (ϵ 13450) in the case of /7/ and λ max. 290 nm (ϵ 11410)

and 230 nm (ϵ 11200), in the case of /8/, which are the characteristic absorptions shown by the two corresponding cyclic derivatives /30/ and /31/, (see fig. 4). In dilute methanolic solution there is stabilization of the lactam form of these 2-imidazolin-5-one derivatives; the differences in the absorptions of /7/ and /8/ with /30/ and /31/ could therefore be detected easily.

The examination of the infrared spectra (see table 1, fig. 5) shows two broad bands in the NH stretching region at 3400 and 3060 cm^{-1} (for /7/). The first band should arise from (NH) stretching frequency due to amidine group, while the second band should arise from NH_3^+ stretching mode (81, 82). The lower OH frequencies in different chelated compounds have already been observed by many workers, (76-80). Similar low OH frequencies have been found in these syn(NH_2)-(OH)(OC_2H_5) amidines (Z Isomers).

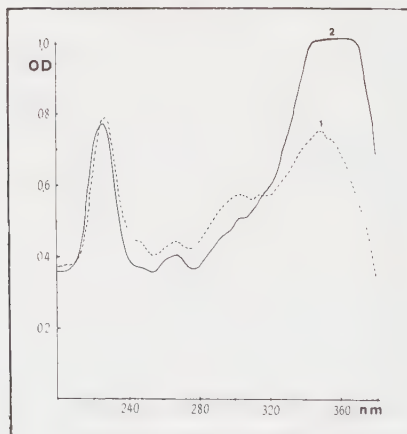


Fig 3 : Ultraviolet absorption spectra (in methanol)

Curve 1 : N-(1-benzyl-2-ethoxy-2-hydroxyvinyl)-
(Z)-2-benzothiazolecarboxamidine /7/

Curve 2 : N-(2-Ethoxy-2-hydroxy-1-isobutylvinyl)-
(Z)-2-benzothiazolecarboxamidine /8/.

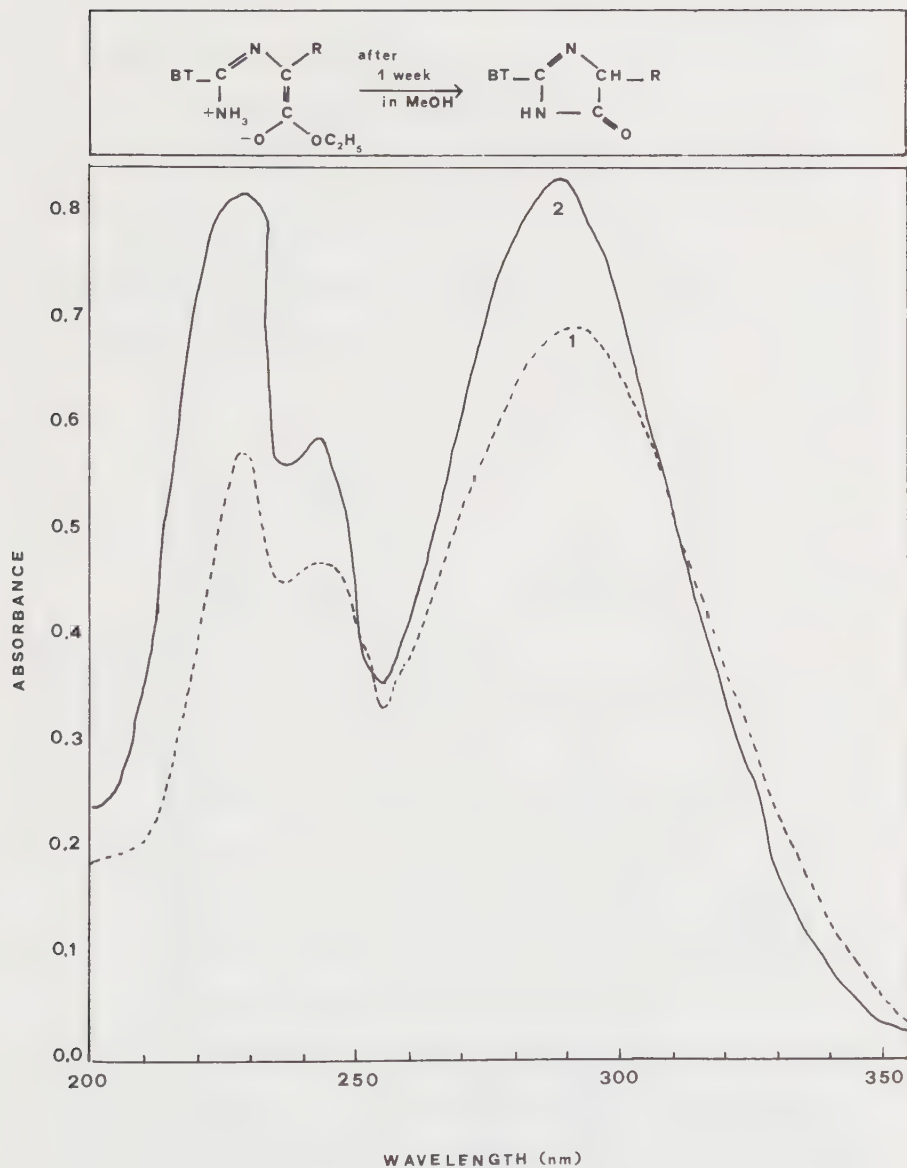


Fig 4 : Ultraviolet absorption Spectra (in methanol) :

Curve 1 : 2-(2-Benzothiazolyl)-4-benzyl-2-imidazolin-5-one /30/,
 (R = $-\text{CH}_2-\text{C}_6\text{H}_5$); Curve 2 : 2-(2-benzothiazolyl)-4-isobutyl-2-
 imidazolin-5-one /31/, (R = $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$).

The total lack of stretching vibration of a normal carbonyl ester grouping confirms our proposed enolic structure. The two medium bands around 1620 and 1592 cm^{-1} should arise from amidine I stretching vibrations. A strong band at 1540 cm^{-1} is probably associated with NH_3^+ deformation (133, 134)

NMR examination of these amidines could not be carried out due to their insufficient solubility in usual solvents. In solvents like deuterated dimethyl sulphoxide these Z-isomers cyclize.

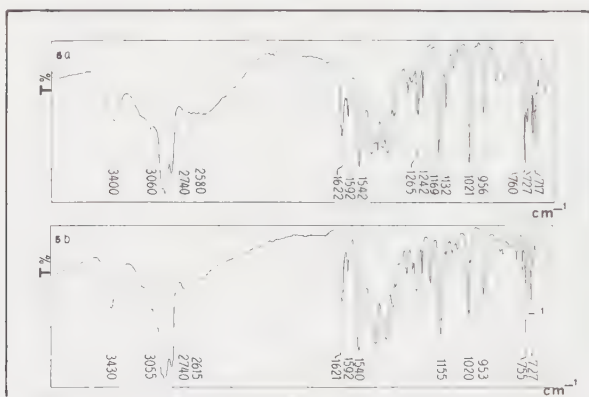
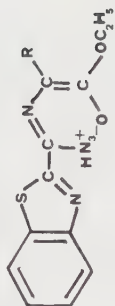


Fig 5 : Infra-red spectra of (5a):N-(1-Benzyl-2-ethoxy-2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamidinium/7/; (5b):N-(2-Ethoxy-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarboxamidinium/8/.

When an optically active α -amino acid ester was used in the condensation with benzothiazole-2-carbonitrile the resulting product, syn(NH_2)-(OH)(OR) amidine (Z isomer) showed no optical activity as could be expected. This is the consequence of the enolic structure of the molecule, since to achieve this enolization the α -carbon atom has undergone a change from sp^3 to sp^2 hybridization state thus increasing the number of conjugated double bonds in the molecule which possess now an almost planar framework.

TABLE 1

Characteristic Frequency Assignment (cm^{-1}) in the Infrared Spectra of N-monosubstituted 2-Benzothiazolecarboxamides. Syn(NH_2)-(OH)(OC_2H_5) Amidines (Z Isomers) (Nujol Mulls)



Compd. No.	R	ν (NH) ν (NH) ₂	ν (OH)	Amidine I ν_{as} (N=C-N)	δ (NH ₃ ⁺)	ν (C=O)	ν (C-OH)	δ (C-H) Aromatic
/7/	$-\text{CH}_2\text{C}_6\text{H}_5$	3400 mb 3060 mb	2740 2580 ^{mb}	1622m 1592m	1542s	1169s 1132m sh	1021s 956 m	760s 727 m 718 m
/8/	$-\text{CH}_2=\text{CH}(\text{CH}_3)_2$	3430 mb 3055 mb	2740 2615 ^{mb}	1621m 1592w	1540s	1155m	1020m	755m 727m
/9/	$-\text{CH}_3$	3425 m 3160 ^{mb} 3058	2738 2670 ^{mb} 2525	1630m 1593m	1546s	1157s	948m	753m 723m

Syn(NH₂)-(OH)(OH) amidines. (Z Isomers)

The isomerization of anti-(NH₂)-t-butyl ester derivatives of amidines in the presence of HBr in glacial acetic acid to give syn(NH₂)-(OH)(OH) amidine monohydrobromides, has already been described. These /10/, /12/, /13/ are also intense yellow crystalline products, more stable than their ethyl ester counterparts. But when neutralized with triethylamine, the amidine monohydrobromide gives rise to free amidine base (N-(1-benzyl-2,2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine, /11/), which has very similar properties to those of syn(NH₂)-(OH)(OC₂H₅) amidine. It easily cyclizes as free base to afford 2-imidazolin-5-one derivative /30/. On the other hand we can explain the stabilization of this molecule by its dipolar structure.

The ultraviolet spectra of these compounds show similar absorptions as syn(NH₂)-(OH)(OC₂H₅) amidines. The molar extinction coefficients are about four times higher in the first two cases compared with those of syn-(NH₂) enolic ester amidines.

/10/	λ max. 210 nm (ε 41440) , 354 nm (ε 46720)	see <u>Fig 6</u>
/11/	λ max 213 nm (ε 42610) , 357 nm (ε 41320)	
/12/	λ max. 214 nm (ε 14640) , 355 nm (ε 22070)	see <u>Fig 6</u>
/13/	λ max. 208.5nm(ε 17080) , 354 nm (ε 22830)	

These higher absorptions should arise from the multiple conjugated bonds system.

The infrared spectra described in Table 2 by their major and characteristic absorption bands, were obtained as nujol mulls (see also Fig 7).

A broad medium band in the first three cases has been assigned to NH stretching vibrations. The low OH frequencies

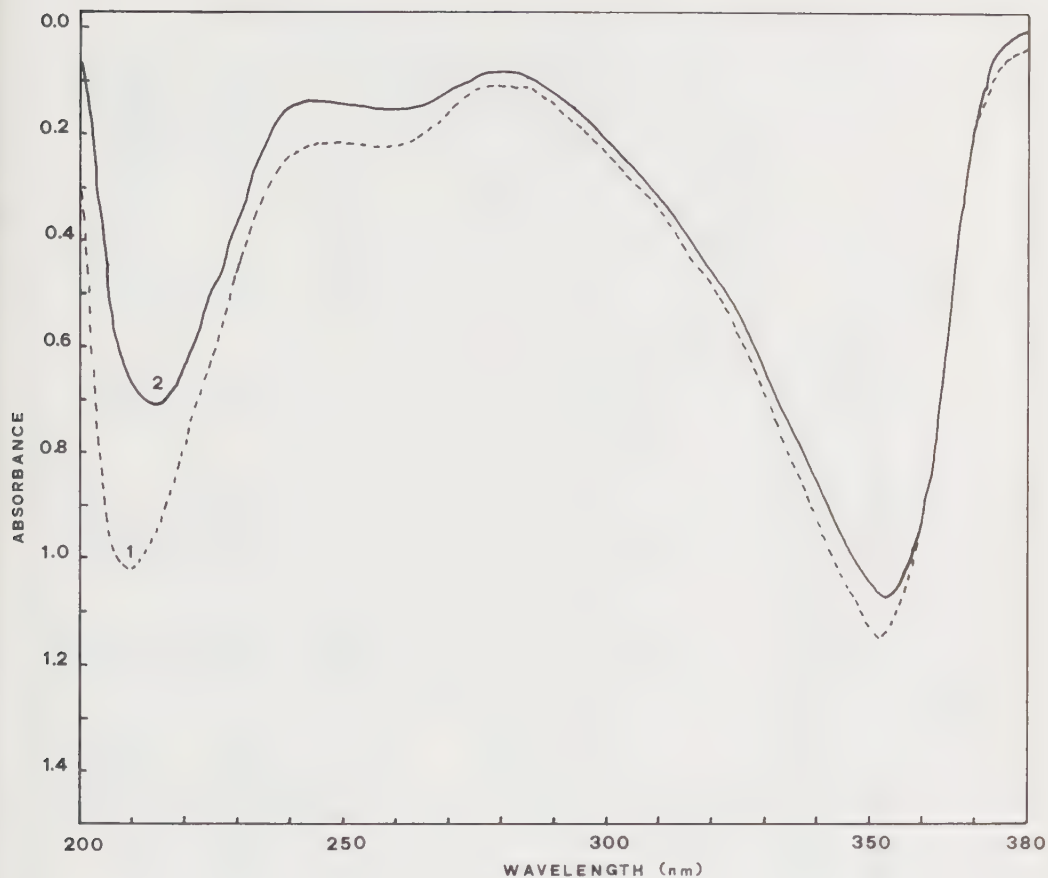
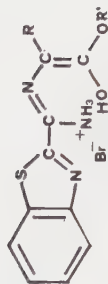


Fig 6 : Ultraviolet absorption spectra (in methanol)

Curve 1 : N-(1-Benzyl-2,2-dihydroxyvinyl)-(Z)-2-benzothiazole-carboxamidine, monohydrobromide /10/ ; Curve 2 : N-(2,2-Dihydroxyvinyl-1-methyl)-(Z)-2-benzothiazolecarboxamidine, monohydrobromide /12/.

TABLE 2

Characteristic Frequency Assignment (cm^{-1}) in the Infra-red Spectra of
 N-monosubstituted 2-Benzothiazolecarboxamides. $\text{Syn}(\text{NH}_2)\text{-(OH)(OH)}$ and
 $\text{Syn}(\text{NH}_2)\text{-(OH)(Br)}$ Amidines, monohydrobromides, (Z Isomers).
 (Nujol mulls)



Comp. No.	R	R'	ν (N-H)	ν (O-H)	Amidine I ν_{as} (N=C-N)	δ (NH_3^+)	Benzothiazole	ν (C-O)	NH_3^+ rocking	Arom. δ (C-H)
/10/	$-\text{CH}_2-\text{C}_6\text{H}_5$	OH	3360m	2735 $\left\{ \begin{array}{l} \text{m, b} \\ \text{m, b} \end{array} \right.$ 2600	1660m 1594m	1551m	1497m	1167m	930 w	767m 748m 732m 715m
/11/	$-\text{CH}_2-\text{C}_6\text{H}_5$ (Free base)	OH	3400 m		1624m 1595m	1547m	-	1170m	1022m	760m 720m
/12/	$-\text{CH}_3$	OH	3380m	2733 $\left\{ \begin{array}{l} \text{m, b} \\ \text{m, b} \end{array} \right.$ 2615 2550	1667s 1593w	1555m 1525m	1500w	1165w	938w	769m 731w 700w
/13/	$-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	Br		2720 $\left\{ \begin{array}{l} \text{m, b} \\ \text{m, b} \end{array} \right.$ 2638	1652m 1600m 1586m	1554m 1529w, sh	1488s	1290m 1250m 1079m	889w	754m 725w 699m

arise in the same region as the syn(NH₂)-enolic ester derivatives. The bands around 1667 cm⁻¹ and 1586 cm⁻¹ have been assigned to amidine I stretching vibrations ($\nu_{as}(N=C-N)$). These bands may arise from amidine grouping as well as the heterocyclic C=C or C=N vibrations. But normal benzothiazole frequencies are comparatively of lower intensities. The band around 1550 cm⁻¹ has been assigned to NH₃⁺ deformation modes.

The absence of normal C=O frequency of the acid function confirms our proposed enolic structure to these compounds. The C-O stretching vibrations are found around 1165 cm⁻¹.

The medium bands which appear in the region 769-699 cm⁻¹ in the spectra are due to the out-of-plane deformation vibrations of the hydrogen atoms on the benzothiazole ring.

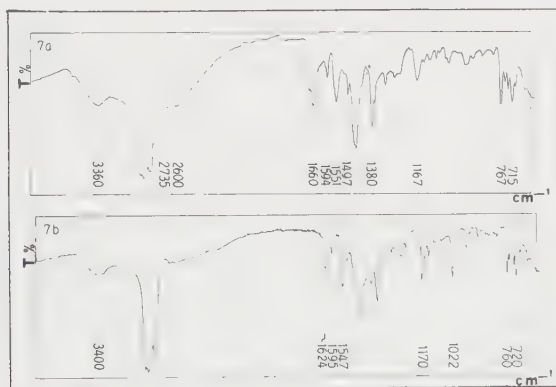
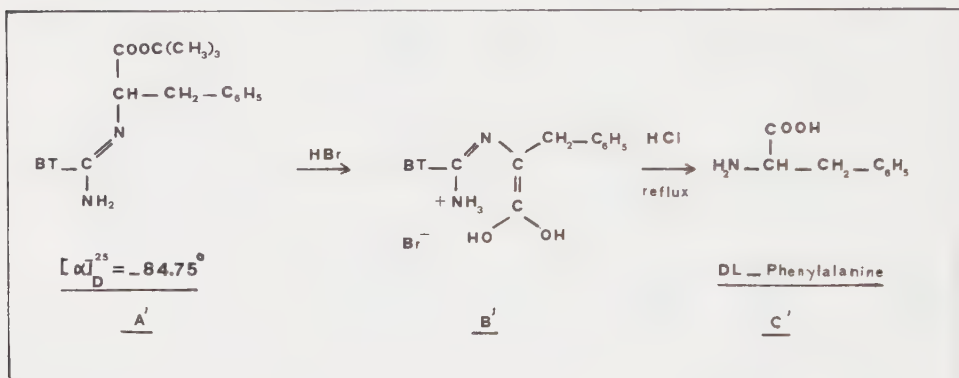
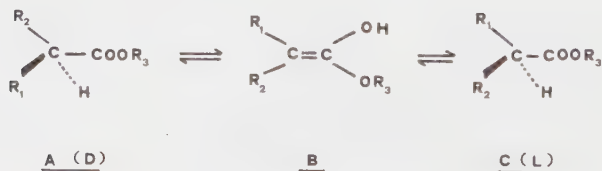


Fig 7 : Infra-red spectra of **(7a):** N-(1-Benzyl-2,2-dihydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine, monohydrobromide /10/ ; **(7b):** N-(1-Benzyl-2,2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine /11/. (Nujol mull)

We used an optically active anti(NH₂) amidine (t-butyl ester substituent) as the starting material in the reaction of acidolysis. If, as we assumed it, the product is enolized the α -carbon atom must have undergone a change from sp^3 to sp^2 hybridization state and the resulting multiple conjugated double bonds system must be planar. Therefore B' should have no optical activity. This was confirmed experimentally.



Considering a molecule A (136-142) possessing an asymmetric carbon atom in the α -position of a group capable of undergoing a tautomeric change, as in the following equation:



Enolization will destroy the asymmetry of the molecule and when the enol form reverts to the keto form the probabilities to do it towards the L or the D forms are equal, resulting in a racemic modification.

Therefore the hydrolysis of B', restoring the sp^3 hybridization state of the α -carbon atom, should lead to a racemic product, the probability to get whether the L or the D forms being equal. The hydrolysis of B' carried out with 6N HCl at reflux for 15 hrs yielded DL-phenylalanine, confirmed by comparison with an authentic sample.

ANTI (NH₂)- AMIDINES. (E ISOMERS)

Ethyl ester and t-Butyl ester Derivatives.

In all 9 anti-(NH₂) amidines (E isomers) are described. The preparation of these isomers by the reaction between an α -amino acid ester and benzothiazole-2-carboximide (or its hydrochloride) in ether (or methanol-ether mixture) as the solvent at ambient temperature has been discussed in the experimental part. In these preparations the speed of the reaction can be raised appreciably by the use of an acid catalyst or by increasing the methanol-ether ratio for the reaction medium.

The anti-(NH₂) amidines are white crystalline products. Some of them melt without isomerization at their melting point temperature. Thus, N-(amino-2-benzothiazolylmethylene)-3-phenyl-ethyl ester, (E)-L-alanine, /14/, melts at 138-140°. When the melt was held for about 15 minutes at 140°, it yielded a yellow coloured product. The infrared spectrum of this yellow product confirmed that it is 5-hydroxy-2-imidazole derivative (/30/-Enol form; for i.r. see table 5)

Another curious anti-(NH₂) amidine, N-(amino-2-benzothiazolylmethylene)-ethyl ester, (E)-glycine, /16/, is thermodynamically very stable. Its melting point is 114-118° and when sublimed at 70° (0.01 mm Hg), it did not undergo any structural change. But the mass spectral data revealed that a cyclisation took place while recording. Comparatively the compounds /15A/, /17/, /18/, /19/, undergo more easily a thermic isomerization to give their corresponding cyclic derivatives. The anti-(NH₂)-t-butyl ester derivatives isomerize in the presence of hydrobromic acid in glacial acetic acid to give syn(NH₂)-(OH)(OH) amidinium bromides.

When optically active α -amino acid esters have been

used in the synthesis, the optical rotation has been observed in the yielding amidine counterpart revealing retention of configuration.

The ultraviolet spectrum shows two absorption maxima around 207 and 280 nm. (Fig 8)

Compd.
No.

/14/	λ max.	207.5 nm (ϵ 30980), 280 nm (ϵ 16900)
/15/	λ max.	207.5 nm (ϵ 22350), 280 nm (ϵ 16350)
/20/	λ max.	206.5 nm (ϵ 31880), 281 nm (ϵ 16540)

The infrared spectral examination of these compounds reveals the presence of amino-form of amidines. For all of them the spectra were carried out as nujol mulls and for five of them they were also performed on the solutions. The characteristic frequencies are given respectively in Table 3 and Table 4.

In the NH stretching region (nujol mulls), no two peaks are observed in all cases (/14/,/15/), instead four bands are seen. There may be many possible reasons, as such multiple bands may arise from dimeric forms or tautomeric forms or may be due to hydrogen bonding in the molecule. But in most cases two medium bands arise from NH asymmetric (higher frequency band) and NH symmetric (lower frequency band) stretching vibrations are observed.

The carbonyl (C=O) ester stretching frequencies are at their normal positions in all cases. The C=N and C=C region is a matter of little discussion. Both of these stretching vibrations can arise either from heterocyclic part or from the lateral amidine grouping. The single strong or medium band is found around 1512 cm^{-1} in all cases. This band is probably best described as the heterocyclic (benzothiazole) vibrations. The band at this frequency region has been observed in many of the common functional 2-substituted

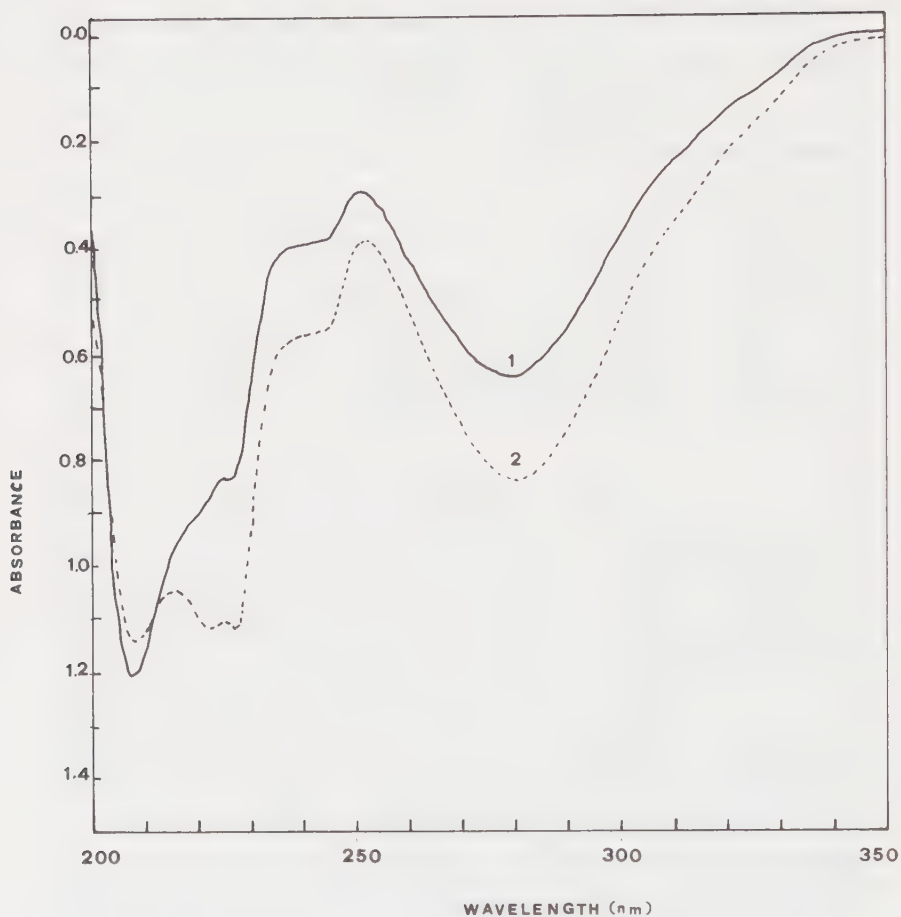


Fig 8 : Ultraviolet absorption spectra (in methanol)

Curve 1 : N-(Amino-2-benzothiazolymethylene)-3-phenyl-ethyl ester, (E)-L-alanine /14/; Curve 2 : N-(Amino-2-benzothiazolymethylene)-ethyl ester, (E)-DL-leucine /15A/.

benzothiazole derivatives, wherein there is no other possibility but its own vibration mode. The C-O stretching frequency band varies between $1246-1160\text{ cm}^{-1}$. In certain cases more than one band have been observed. The bands near 750 cm^{-1} have been assigned to out-of-plane deformations of the CH on the benzothiazole.

The i.r. solution spectra show a more clear picture. Of the five cases studied, only one compound (/18/) in chloroform shows a very weak band at 3300 cm^{-1} . This has been attributed to NH of the imino nitrogen (=N-H). But when compared with ν as and ν s(NH_2) stretching frequencies the contribution of this band can be considered negligible.(see discussion on N-alkyl,N-aryl amidines)

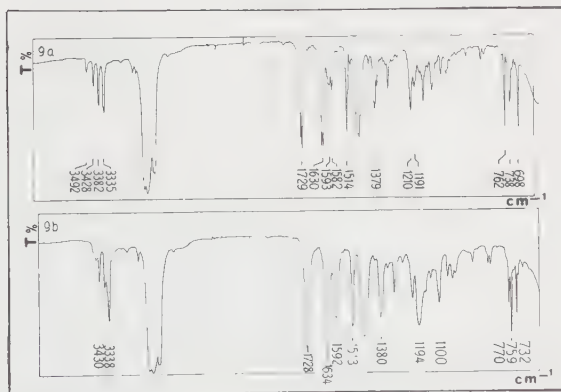
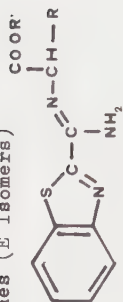


Fig 9 : Infra-red spectra of (9a): N-(Amino-2-benzothiazolymethylene)-3-phenyl-ethyl ester, (E)-L-alanine /14/ ; (9b) : N-(Amino-2-benzothiazolymethylene)-ethyl ester, (E)-DL-leucine /15A/. (Nujol mull)

TABLE 3

Characteristic Frequency Assignment (cm^{-1}) in the Infrared Spectra of

N-monosubstituted 2-Benzothiazolecarboxamides, Anti-(NH_2) Amidines (E Isomers)
(Nujol Mulls)



Compd. No.	R	R'	$\nu(\text{NH}_2)$ 1 as 2 s	$\nu(\text{C=O})$	$\nu(\text{C=N})$	Amidine I $\nu(\text{N=C-N})$ as	Benzothiazole	$\nu(\text{C-O})$	$\delta(\text{C-H})$ Arom.
/14/	$-\text{CH}_2-\text{C}_6\text{H}_5$	$-\text{C}_2\text{H}_5$	3498 w 3435 m 3385 m 3340 m	1729 m	1631 s	1595 m 1583 s	1518 m	1211 m 1193 m	762 m 738 m 698 m
/15A/	$-\text{CH}_2-\text{CH}(\text{CH}_3)$	$-\text{C}_2\text{H}_5$	3462 w sh 3430 w 3380 w sh 3340 m	1730 s	1635 s	1593 m	1516 m	1227 m 1195 m b	772 m 760 m 734 m
/16/	H	$-\text{C}_2\text{H}_5$	3455 m 3338 m	1731 s	1643 s	1607 m	1512 m	1211 s	762 m 737 m
/17/	$-\text{CH}(\text{CH}_3)_2$	$-\text{C}_2\text{H}_5$	3477 m 3372 s	1722 s	1628 s	1593 s	1512 m	1197 s	760 s 734 s
/18/	$-\text{C}_6\text{H}_5$	$-\text{C}_2\text{H}_5$	3459 m 3353 m	1730 s	1632 m	1595 m	1511 m	1205 m	765 m 735 m 700 m
/19/	$-\text{COOC}_2\text{H}_5$	$-\text{C}_2\text{H}_5$	3450 m 3345 m	1743 s 1731 s	1658 m sh 1645 s	1603 m 1595 sh	1518 m	1227 m 1182 m 1163 m	769 m 765 s 738 m

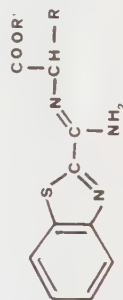
contd

Compd. No.	R	R'	$\nu(\text{NH}_2)$ 1 as 2 s	$\nu(\text{C=O})$	$\nu(\text{C=N})$	Amidine I $\nu(\text{N=C-N})$ as	Benzothiazole	$\nu(\text{C-O})$	$\delta(\text{C-H})$ Arom.
/20/	$-\text{CH}_2\text{C}_6\text{H}_5-$	$-\text{C}(\text{CH}_3)_3$	3450 s 3355 s	1720 s	1635 s	1597 s	1513 s	1232 s 1160 s	761 s 743 s 732 s 700 s
/21/	$-\text{CH}_3$	$-\text{C}(\text{CH}_3)_3$	3435 m 3325 m	1728 s	1635 s	1602 m 1593	1512 m	1230 m 1161 m	763 s 732 m
/22/	$-\text{H}$	$-\text{C}(\text{CH}_3)_3$	3445 m 3320 m	1735 s	1638 m	1607 m 1598	1518 m	1240 m 1228 m 1165 m	784 m 767 m 735 m
/23/	$-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	$-\text{C}(\text{CH}_3)_3$	3465 m 3440 3362 m 3338 m	1722 s	1636 s	1600 m	1517 m	1246 m 1218 m 1163 m	760 m 735 m
/24/	$-\text{CH}(\text{CH}_3)_2$	$-\text{C}(\text{CH}_3)_3$	3458 s 3337 s	1727 s	1640 s	1605 s	1515 m	1160 s	765 s 737 s

TABLE 4

Characteristic Frequency assignment in the 2-7 μ region of Anti-(NH₂) Amidines (ethyl ester and t-butyl ester derivatives) of N-monosubstituted 2-benzothiazolecarboxamidines in solution.

Compd. No.	Solvent	R*	R	ν (NH ₂) ν_{as} ν_s		ν (=NH)	ν (C=O)	Amidine I ν_{as} (N=C-N)	(C≡C) arom.
/14/	CCl ₄	-C ₂ H ₅	-CH ₂ -C ₆ H ₅	3478w	3378w		1738w		
/18/	CHCl ₃	-C ₂ H ₅	-C ₆ H ₅	3488w	3380w	3300vw	1708w, sh 1740s	1642m 1585w 1647s 1587s 1621s, sh	1478w
/21/	CCl ₄	-C(CH ₃) ₃	-CH ₃	3470vw	3380vw		1742m 1705m, sh	1645m 1585 1620m, sh	1511m
/23/	CCl ₄	-C(CH ₃) ₃	-CH ₂ -CH(CH ₃) ₂	3475w	3378vw		1741m 1701m	1643m 1582m 1618w, sh	1511m
/24/	CS ₂	-C(CH ₃) ₃	-CH(CH ₃) ₂	3475vw	3377vw		1738w 1703w	1642w	



2-IMIDAZOLIN-ONE, 5-HYDROXY-2-IMIDAZOLE, 5-O-ACETYL-2-IMIDAZOLE
DERIVATIVES :

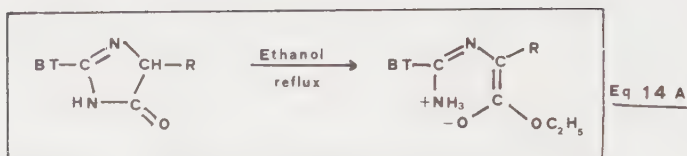
The 2-imidazolin-5-one derivatives have been prepared from their corresponding syn-(NH₂)-(OH)(OC₂H₅) amidines or from syn-(NH₂)-(OH)(OH) amidines (free bases), (Z isomers), wherever possible by sublimation in vacuo (/30/,/31/,/32/,/33/). (Eq 14). Acidic or thermal isomerization of amidino acid (imino form) is also a way to obtain these compounds.

The 5-hydroxy-2-imidazole derivatives were synthesized by the reaction between benzothiazole-2-carbonitrile and an α -amino acid ethyl ester in methanol at reflux (/34/,/35/,/36/). Further, this reaction product on sublimation in vacuo and/or by recrystallization from methanol yielded these 2-imidazolin-5-one derivatives.

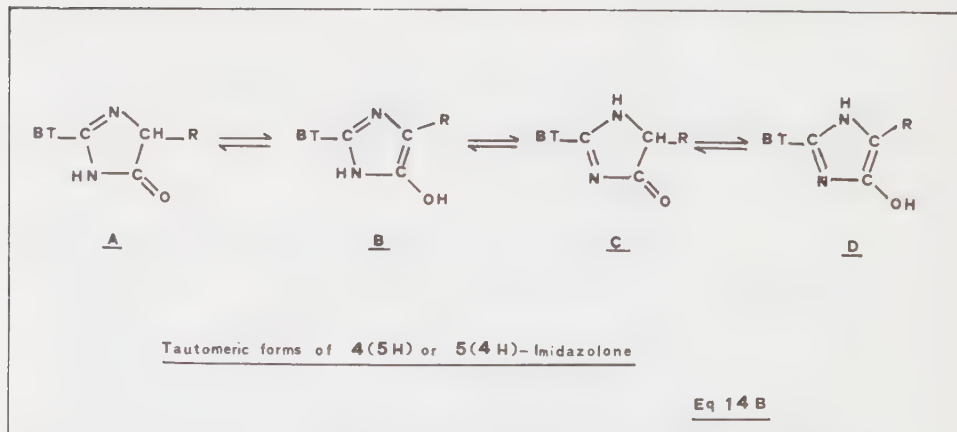
The 5-O-acetyl-2-imidazole derivatives (/37/,/38/) were prepared by the acetylation of syn-(NH₂)-(OH)(OC₂H₅) amidines (/8/,/9/) in the presence of acetic anhydride and glacial acetic acid at room temperature.

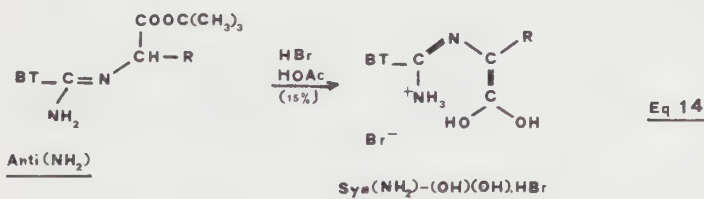
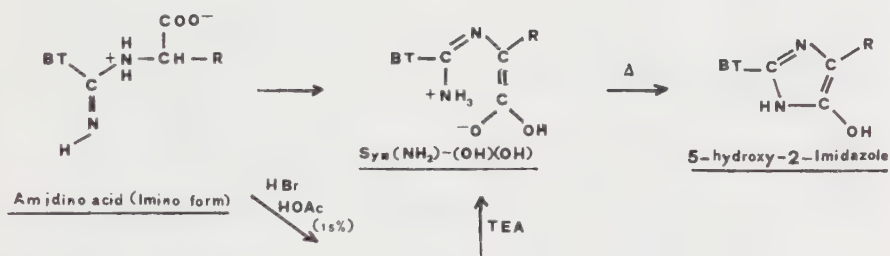
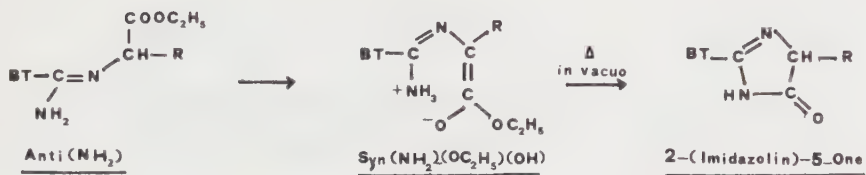
All these cyclic products are quite stable. They are yellow crystalline compounds except the two 5-O-acetyl-2-imidazoles, which are white.

In boiling ethanol the cycle of 2-imidazolin-5-one derivatives can be opened to give their corresponding syn-(NH₂)-(OH)(OC₂H₅) amidines, (see Eq 14 A), This was confirmed by their ultraviolet and infrared spectra



In all four tautomeric forms (A,B,C and D) of 4(5H) or 5(4H) imidazolones are possible (Equation 14B). Out of these A and B forms could be characterized by their infrared spectra. In dilute methanolic solutions the lactam form A seemed to be predominant. (see Fig 4 and 10)





Eq 14

The ultraviolet spectrum shows two absorption maxima in dilute methanolic solution

Compd.
No.

/30/ λ max. 290 nm (ϵ 11410), 230 nm (ϵ 11200) Fig 10 & Fig 4

/31/ λ max. 290 nm (ϵ 12140), 227 nm (ϵ 13450) Fig 4

The results of the infrared spectra are given in the table 5 (nujol mulls).

The NH stretching vibrations are observed at little low frequency, may be resulting from their dimeric structure. These are not well distinct bands being broad ones. The carbonyl (C=O) stretching frequencies are well defined strong bands in the case of 2-imidazolin-5-one derivatives. The two medium intensity bands near 1618 cm^{-1} and 1588 cm^{-1} can arise from cyclic amidine structure. The third lower frequency band around 1535 cm^{-1} has been attributed to the NH deformation vibrations. The bands near 700 cm^{-1} are assigned due to heterocyclic CH out of plane deformation vibrations.

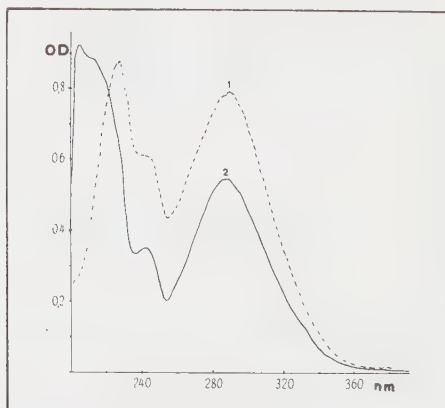


Fig 10 : Ultraviolet absorption spectra (in methanol) :

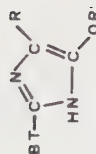
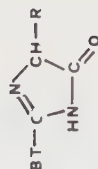
Curve 1 : 2-(2-Benzothiazolyl)-4-benzyl-2-imidazolin-5-one /30/;

Curve 2 : 2-(2-Benzothiazolyl)-4-methyl-2-imidazolin-5-one /32/.

TABLE 5

Positions of absorption maxima (cm^{-1}) in the infrared spectra of 2-(2-Benzothiazolyl)-imidazolin-5-one and 2-(2-Benzothiazolyl)-5-hydroxy-imidazole. (nujol mulls)

Compd.No.	R	R [*]	ν (N-H)	ν (O-H)	ν (C=O)	ν Amidine	δ (N-H)	δ (C-H) arom.
/30/	$-\text{CH}_2-\text{C}_6\text{H}_5$		3200-3100 b		1727s	- 1618m 1588m	1535m	-758m 737m, 695m
/31/	$-\text{CH}_2-(\text{CH}_3)_2$		3200-3100 b		1725s	- 1618s 1590m	1530s	-753s, 721m
/32/	$-\text{CH}_3$		3320m 3150m		1737m	- 1622m 1588m	1535m	-750m, 717m
/33/	$-\text{CH}(\text{CH}_3)_2$		3170m, b		1735s	- 1617m 1590m	1505m	-759m, 722m
/30/	$-\text{CH}_2-\text{C}_6\text{H}_5$	H	3442m	- 2725 _{yw} 2670 _b	-	- 1623m 1592m	1549m	-759m 732m, 709m
/34/	$-\text{COOC}_2\text{H}_5$	H	3220m	- 2667m, b 2590m, b	1678s	- 1592m 1562m	1515m	-754m, 725m
/35/	$-(\text{CH}_2)_2\text{COOC}_2\text{H}_5$	H	3305m	- 2700m, b	1707m	- 1633m 1594m	1549m	-765m, 743m 732m, 719m
/36/	$-\text{C}_6\text{H}_5$	H	3420m, sh 3402m	- 2730m, b 2570m, b	-	- 1600m 1592m, sh 1615m	1544m	-775m, 765m 760m, 730m
/37/	$-\text{CH}_3$	$-\text{COCH}_3$	3380m	-	1767s 1756s	1594m	1548m	-768m, sh 761m, 729m
/38/	$-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	$-\text{COCH}_3$	3240m	-	1750s	- 1612m 1593vw	1538m	-760m, 733m 708m



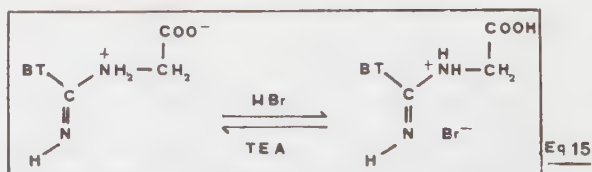
AMIDINO ACIDS (IMINO FORM). (Zwitterionic Derivatives):

N-monosubstituted amidino acids (Imino form) were synthesized by the action of lithium salts of α -amino acids on the benzothiazole-2-carboximide in methanol as a solvent at reflux. Subsequent neutralization of the lithium salt of amidino acid gives zwitterionic amidino acid containing imino form of amidine.

The amidino acids are very less soluble in most of the solvents, resembling in many ways α -amino acids. They are high melting white to off-white solids. They isomerize on their melting to yield cyclic derivatives, except the amidino acid of glycine (/25/), which decomposes.

All of them in the presence of hydrobromic acid in glacial acetic acid isomerize to give syn(NH₂)-(OH)(OH) amidinium bromide derivatives. They show the same chemical, physical and spectral characteristics as the one obtained by the isomerization of anti-(NH₂) t-butyl ester derivatives in the same reaction conditions. Here also glycine derivative is an exception. This amidinium bromide (/61/ : N-(imino-2-benzothiazolylmethyl)-glycine, monohydrobromide) retains its normal carboxylic acid function, which is confirmed by its infrared spectrum. Its ultraviolet spectrum is very resembling to amidino acid counterpart. (see fig. 12)

On this basis we can confirm that the two compounds have the same structural grouping (Imino form of amidine). The additional evidence comes from their interconversion in the presence of hydrobromic acid and triethylamine, (Eq 15).



Hence the compound /61/ can be included in this serie of amidino acids (Imino form).

The ultraviolet spectra of these isomers show three absorptions maxima. The dilute methanolic solutions show the following λ max. for the said compounds: (Fig 11 -12)

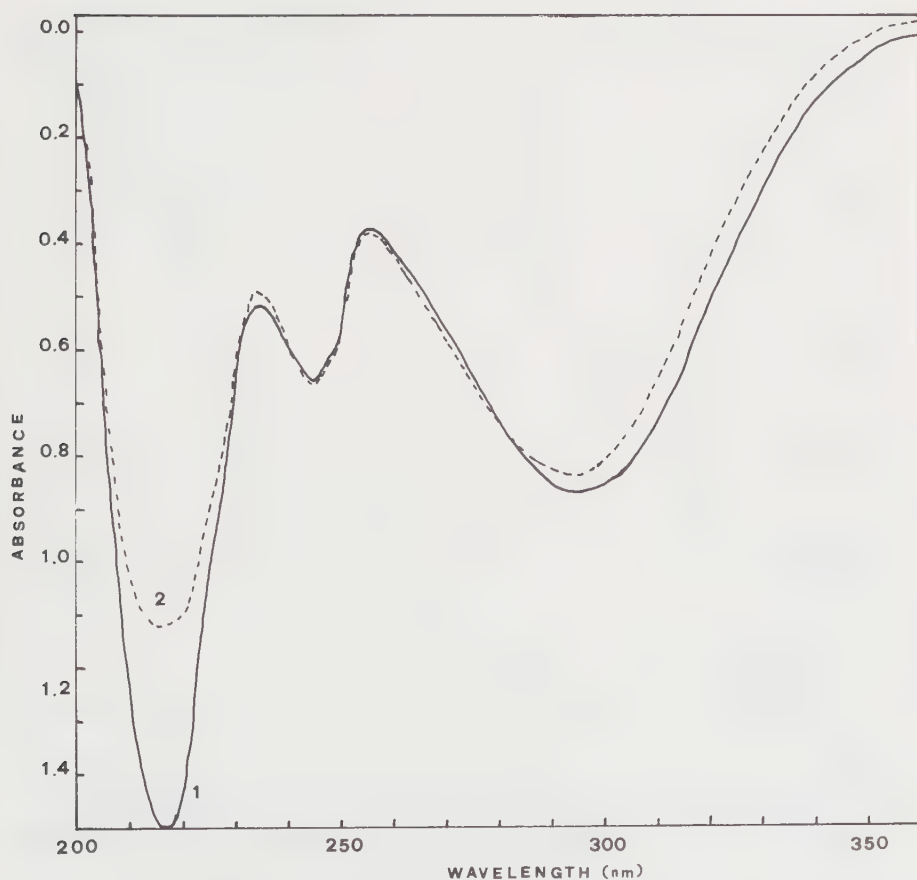


Fig 11 : Ultraviolet absorption spectra (in methanol)

Curve 1 : N-(Imino-2-benzothiazolymethyl)-DL-phenylalanine
/27/ ; Curve 2 : N-(Imino-2-benzothiazolymethyl)-L-alanine
/26/.

Compd.
No.

/26/ λ max. 215 nm (ϵ 16340), 245 nm (ϵ 9694), 294 nm (ϵ 12260)

/27/ λ max. 217 nm (ϵ 21326), 245.5nm(ϵ 9355), 295 nm (ϵ 11658)

/29/ λ max. 212 nm (ϵ 19694), 245.5nm(ϵ 11064), 297 nm (ϵ 14384)

/25/ λ max. 212 nm (ϵ 15666), 244.5nm(ϵ 9487), 295 nm (ϵ 12285)

/61/ λ max. 208.5nm(ϵ 18750), 244 nm (ϵ 10350), 298 nm (ϵ 12390)

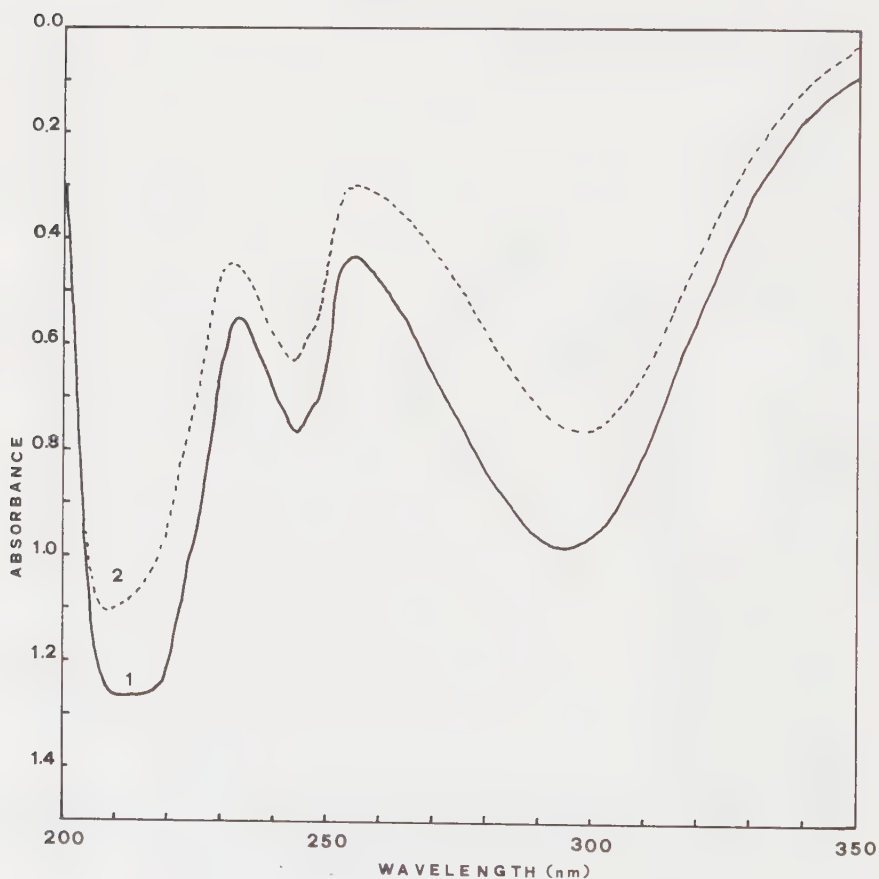
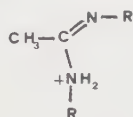


Fig 12 : Ultraviolet absorption spectra (in methanol)

Curve 1 : N-(Imino-2-benzothiazolylmethyl)-glycine /25/;

Curve 2 : N-(Imino-2-benzothiazolylmethyl)-glycine, mono-hydrobromide /61/.

The infrared spectral examination of these compounds shows the presence of imino-form of amidines. The characteristic infrared absorption frequencies are summarized in the table 6. The NH stretching frequency region is a matter of some discussion. The single band which appears near 3300 cm^{-1} can arise from the NH of the dicoordinate nitrogen ($=\text{N-H}$) or the tricoordinate nitrogen ($-\text{NH}-$) group. But as the compound exists as a zwitterion, we can expect on the basis of theoretical and experimental evidence (83-86), an extra proton to be attached on the imino nitrogen. Prevorsek (87,88) has studied amidinium cations and has suggested the following structure for some N,N'-disubstituted amidine hydrochlorides, on the basis of their infrared spectra. And he has assigned the



band at 3310 cm^{-1} to the vibration of the $=\text{N-H}$ group in the case of N-diethyl amidine derivatives (89). The band in this region of our spectrum most probably arise from the vibrations of the $=\text{N-H}$ group. The low frequency (NH^+) absorptions are in accordance with NH_2^+ stretching vibrations (90-92).

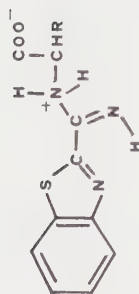
The medium shoulder band near 1670 cm^{-1} can be assigned to C=N group of the amidinium function. The strong band around 1610 cm^{-1} has been assigned to the vibrations of COO^- group. (93). The strong band near 1540 cm^{-1} can be attributed to the NH deformation vibrations. The C-N stretching frequencies are observed near 1340 cm^{-1} , (94). The C-O stretching bands are found in the range of $1043-1078\text{ cm}^{-1}$. The medium intensity band around 900 cm^{-1} can be explained only if we suppose that it occurs from a $-\text{NH}_2^+$ group of the N-substituted α -amino acid (Amidino acid, imino form) since

TABLE 6

Positions of absorption maxima (cm^{-1}) in the infrared spectra of

N-mono-substituted 2-benzothiazolecarboxamidines.

AMIDINO ACIDS (IMINO FORM). ZWITTERIONIC DERIVATIVES.



(Nujol mulls)

Compd. No.	R	$\nu(\text{=NH})$	$\nu(\text{NH}_2^+)$	$\nu(\text{C=N})$	$\nu(\text{COO}^-)$	$\delta(\text{N-H})$	$\nu(\text{C-N})$	$\nu(\text{C-O})$	$\nu(\text{NH}_2^+)$	$\delta(\text{C-H})$ arom.
/25/	-H	3320s	2680m, b		1662s	1540m	1333s	1078m 1043m	930m 902m	760s 752s 728m 688m
/26/	-CH ₃	3300m	2725m, b 2670m, b		1613s	1545s	1340s	1051w	911m 885m	765m 717m
/27/	-CH ₂ -C ₆ H ₅	3315m	2665m	1668m, sh	1600s	1547s	1353s 1329m, sh	1050m	875m 825w, sh	760s 703s
/28/	-CH(CH ₃) ₂	3238m	2635m, b	1675m, sh	1616s	1532s	1340s	1043m	-	767s 735
/29/	-CH(CH ₃) ₂ -CH ₂ -CH ₃	3287m	2720m, b 2670m, b	1665m, sh	1608s	1530s	1345s 1334s		878m	770s 720m

this frequency is in the region of the single bond vibrations. Thus on the basis of the ir spectrum we can admit that the most probable protonation site is the tricoordinate nitrogen instead of the dicoordinate nitrogen, whose protonation would result in a $=NH_2^+$ group which could hardly justify the presence of the band at 900 cm^{-1} . The bands around 750 cm^{-1} have been assigned due to out-of-plane deformations of the CH on the aromatic cycle.

N-alkyl, N-alkylaryl, and N-aryl monosubstituted 2-benzothiazole-carboxamidines:

A specific general procedure for the preparation of these simple amidines is given in the experimental part. Their melting points, recrystallizing solvents and elemental analysis can also be found in the table 10 . All of them are stable solid compounds having sharp melting points. Geometrical isomerism (if it exists) was not observed in these compounds, instead a predominant tautomer in the equilibrium mixture in dilute solution has been established.

The ultraviolet absorption spectra of four of these isomers show three absorption maxima. In dilute methanolic solution the compounds /49/ and /50/ show very similar type of absorptions already found in the case of the amidino acid (imino form) derivatives. λ max. for the said compounds are:

/49/. N-(1-Phenethyl)-2-benzothiazolecarboxamidine:

λ max. 208.5 nm (ϵ 11030), 243 nm (ϵ 8541), 281 nm (ϵ 11870) ;

/50/. N-2(3-phenpropyl)-2-benzothiazolecarboxamidine:

λ max. 209 nm (ϵ 25670), 244.5nm (ϵ 11130), 278nm (ϵ 17300);

/51/. N-phenyl-2-benzothiazolecarboxamidine:

λ max. 206 nm (ϵ 31450), 227.5 nm (ϵ 28000), 280 nm (ϵ 15600);

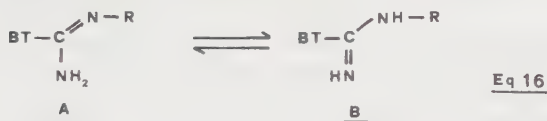
/52/. N-p-tolyl-2-benzothiazolecarboxamidine:

λ max. 208 nm (ϵ 28470), 228.5 nm (ϵ 28540), 280.5 nm (ϵ 15870).

In the above N-aryl compounds, /51/ and /52/, the absorption near 228 nm should arise from (=N-phenyl) group. While the absorption maxima around 244 nm may be assigned due to the imino tautomer in the equilibrium mixture.

The characteristic infrared absorption frequencies (in cm^{-1}) of the twelve compounds can be found in the table 7 (nujol mulls), while ten of them studied in solution are summarized in the table 8.

An simple amidine can be represented in two tautomeric forms A and B in an equilibrium mixture : (Eq 16)



In a dilute solution if these two tautomeric forms exist then we should find more than two absorption bands in the region between $3500\text{--}3150\text{ cm}^{-1}$. If the tautomeric equilibrium had been displaced to the left entirely, two characteristic stretching frequencies due to primary amino group should appear.

Bellamy and Williams (131) have extensively studied the asymmetrical and symmetrical NH stretching frequencies in primary amines. They have shown that in dilute solutions these two frequencies are related by an algebric expression:

$$\nu_{\text{sym}} = 345.53 + 0.876 \nu_{\text{as}}$$

In three N-aryl monosubstituted 2-benzothiazolecarboxamidines we found two NH stretching bands near 3500 and 3385 cm^{-1} . In a similar functional grouping Orville-Thomas and Parsons (132) have observed 3530 cm^{-1} and 3425 cm^{-1} , ν_{as} and ν_{s} NH frequencies in the case of formamidoxime, which infers that N-aryl 2-benzothiazolecarboxamidine most probably contains a terminal amino function. Prevorsek (89) has also confirmed the existence of a terminal amino group in N-phenylamidines. The medium intensity bands in the double bond vibrations region can tentatively be assigned to the amidine

stretching frequencies.

In the N-alkyl 2-benzothiazolecarboxamidines the spectra (for /42/ -/44/ and /46/) contain three bands in the NH stretching frequency region. The two bands near 3500 and 3395 cm^{-1} are much stronger compared to one around 3300 cm^{-1} . The two high intensity bands could arise from the primary amino grouping of an amidine, while the band at 3300 cm^{-1} can be assigned to =NH group. Prevorsek in a similar study has assigned a band near 3305 cm^{-1} to the =N-H absorption, and has proposed that N-alkyl amidines exist predominantly in the form having a terminal imino group. Comparing Prevorsek's results with those of ours will clarify the proposition that N-alkyl 2-benzothiazolecarboxamidines exist predominantly in the amino form of amidine.

From reference (89):	(Frequencies in cm^{-1})		
	ν as(NH_2)	ν (=NH-R)	ν (=NH)
$\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{C}(=\text{NH})\text{NH} \cdot \text{C}_2\text{H}_5$	3510 vw	3448 m	3310 w
$\text{C}_6\text{H}_5 \cdot \text{CH}(\text{CH}_3) \cdot \text{C}(=\text{NH})\text{NH} \cdot \text{C}_2\text{H}_5$	3500 vw	3446 m	3310 w
$\text{C}_6\text{H}_5 \cdot \text{CH}(\text{C}_2\text{H}_5) \cdot \text{C}(=\text{NH})\text{NH} \cdot \text{C}_2\text{H}_5$	3510 vw	3448 m	3332 w

Our results also to be found in table 8

	(Frequencies in cm^{-1})		
	ν as(NH_2)	ν s(NH_2)	ν (=NH)
/42/ BT- $\text{C}(\text{NH}_2)=\text{N} \cdot (\text{CH}_2)_3\text{CH}_3$	3500 w	3395 w	3300 vw
/43/ BT- $\text{C}(\text{NH}_2)=\text{N} \cdot (\text{CH}_2)_2\text{CH}_3$	3500 w	3398 w	3300 vw
/44/ BT- $\text{C}(\text{NH}_2)=\text{N} \cdot \text{CH}_2\text{CH}_3$	3508 w	3395 w	3305 vw

It is also interesting to see the spectra of N-methyl, N-ethyl, N-n-propyl and N-n-butyl in the solid phase (nujol mull) (Fig 13)

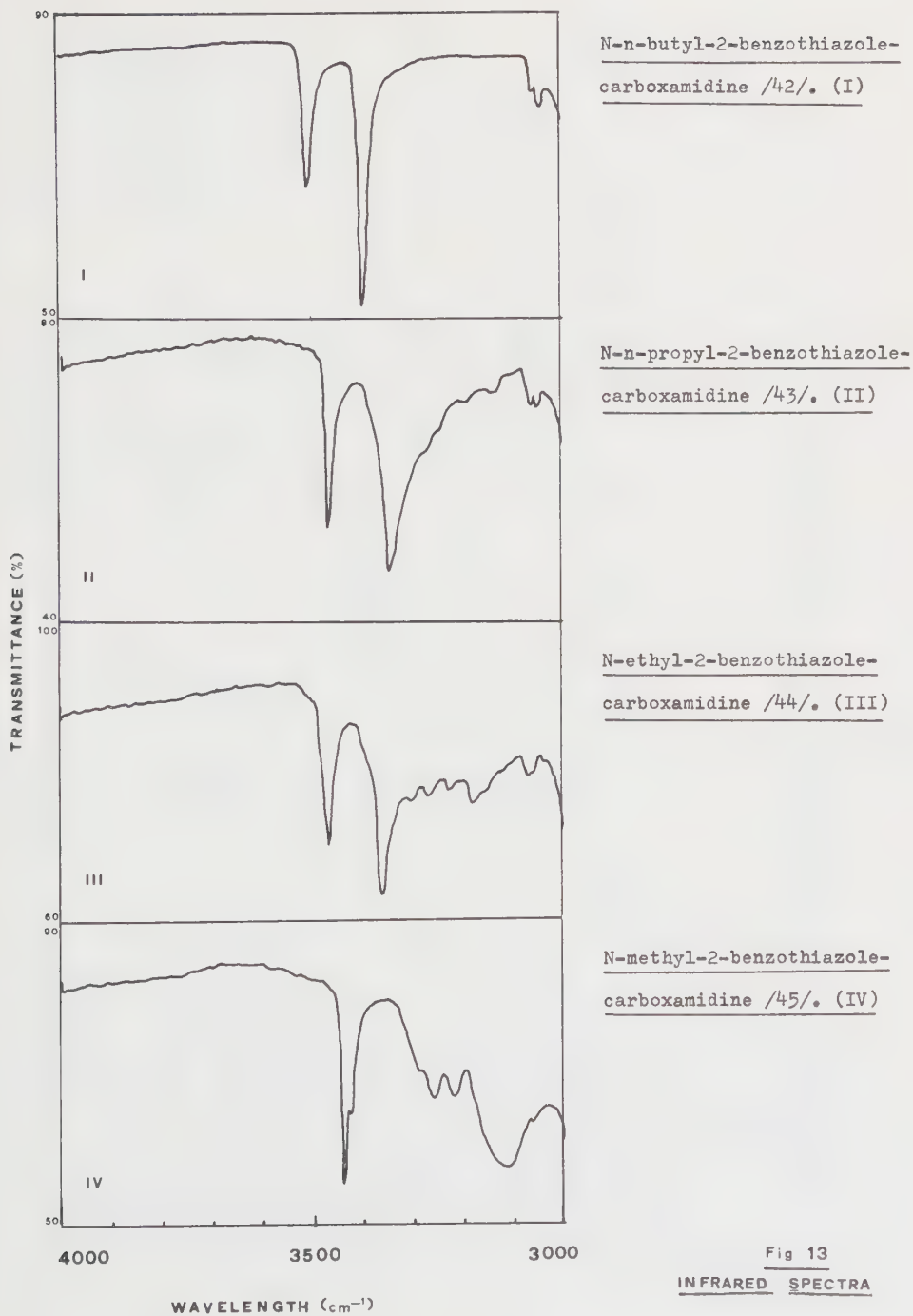
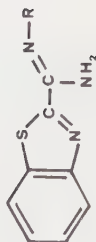


TABLE 7

Positions of absorption maxima (cm^{-1}) in the infrared spectra in the 2-7 μ region of N-alkyl, N-aryllaryl, N-aryl monosubstituted 2-benzothiazolecarboxamides. (Nujol Mulls)



Compound Number	R	$\nu(\text{NH}_2)$			$\nu(=\text{NH})$		Amidine I $\nu_{\text{as}}(\text{N-C-N})$		Benzothiazole
		ν_{as}	ν_s	ν_s					
/42/	$-(\text{CH}_2)_3-\text{CH}_3$	3508m		3498m			1635m	1569m	1510m
/43/	$-(\text{CH}_2)_2-\text{CH}_3$	3468m		3345m			1627m	1583m	1504m
/44/	$-\text{CH}_2-\text{CH}_3$	3468m		3360m	3300, 3270 3228, 3178 vw		1652m sh 1631m	1585m	1507m
/45/	$-\text{CH}_3$	3430w		3250m	3210 sh 3100m		1648s	1608m	1510m
/46/	$-\text{CH}(\text{CH}_3)_2$	3462m		3310m	3255, 3210 3175w		1642m	1588m	1502m
/47/	$-\text{CH}_2-\text{C}_6\text{H}_5$	3490w		3388w			1630m	1572m	1505w
/48/	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_5$	3430m		3318m			1650w	1588w	1510w
/49/	$-\text{CH}(\text{CH}_3)-\text{C}_6\text{H}_5$	3478w		3380w			1634m	1582m	1503m
/50/	$-\text{CH}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_5$	3390m		3252m			1618s	1591w sh	1525s, 1492w
/51/	$-\text{C}_6\text{H}_5$	3438m		3340m			1637m	1583m	1505w, 1486m
/52/	$-\text{C}_6\text{H}_4-\text{CH}_3-p$	3425m		3338m			1645s	1585m	1512m, 1500m
/53/	$-\text{C}_6\text{H}_4-\text{CF}_3-m$	3478m		3343m			1632s 1605m sh	1580m	1515m, 1483m

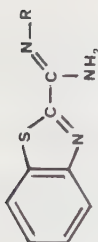


TABLE 8

Characteristic Frequency assignment in the 2-7 μ region of N-alkyl, N-alkylaryl and N-aryl monosubstituted 2-benzothiazolecarboxamide in solution.

+ CCl ₄	+ CHCl ₃	Compd. No.	R	$\nu(\text{NH}_2)$		$\nu(=\text{NH})$	Amidine I $\nu_{\text{as}}(\text{N}=\text{O}-\text{N})$	
ν_{as}	ν_{s}							
/42/*	3500w	3395w	3300	1649w	1620w	1580vw		
/43/*	3500w	3398w	3300vw	1650w	1620w	1580vw		
/44/+	3508w	3395w	3305vw	1653m	1622vw, sh	1580m		
/46/+	3505w	3392w	3305vw	1650m	1618vw, sh	1580m		
/47/+	3503w	3392w		1655m		1582m		
/48/*	3500w	3390w	3300vw	1650s	1620m	1583m		
+	3505w	3395w	3300vw	1652m	1620vw	1581m		
/50/+	3505w	3395w		1650		1580m		
/51/+	3502w	3390w		1648m	1595m	1513m		
/52/*	3495w	3380w		1645m	1612w, sh	1485m		
/53/+	3500m	3385w		1651s		1574m		

wherein the amino form of the amidine is observed in the latter two compounds(/42/ and /43/).

In the amidine I frequency region in the solid phase (nujol mull) two medium bands appear at 1635 cm^{-1} and 1569 cm^{-1} (for /42/) while the same compound in solution shows three bands at 1649 cm^{-1} , 1620 cm^{-1} and 1580 cm^{-1} . Whether the band at 1620 cm^{-1} arises from the form having a terminal imino group?

For the infrared spectra of solutions of three condensation products of benzothiazole-2-carbonitrile with an α -amino acid-t-butyl ester derivative the relation between ν as and ν s NH stretching vibrations proposed by Bellamy and Williams fits quite satisfactorily with a deviation of about 5 to 7 cm^{-1} . This, as well as the consideration of steric hindrance, is in favour of the anti-(NH_2) form propounded for these compounds. (see Table 4)

With all these results together we can conclude saying: All the N-monosubstituted 2-benzothiazolecarboxamides (except the amidino acid (imino form) derivatives) exist predominantly in the amino form of amidine in the equilibrium mixture in dilute solutions.

The NMR examinations were carried out for eight compounds of this serie. The chemical shifts are given in δ ppm.

N-n-butyl-2-benzothiazolecarboxamidine . /42/ : (CDCl_3)

0.91 (d, 3H, $-\text{CH}_3$) ; 1.57 (m, 4H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$) ; 3.25 (t, 2H, $=\text{N}-\text{CH}_2$) ; 5.75 (s, broad, 2H, $-\text{NH}_2$) ; 7.42-7.93 (m, 4H, 2-benzothiazolyl)

N-n-propyl-2-benzothiazolecarboxamidine. /43/ (CDCl_3)

1.03 (t, 3H, $-\text{CH}_2-\text{CH}_3$) ; 1.76 (m, 2H, $-\text{CH}_2\text{CH}_3$) ; 3.21 (t, 2H, $=\text{N}-\text{CH}_2$) ; 5.91 (s, broad, 2H, $-\text{NH}_2$) ; 7.44-7.97 (m, 4H, 2-benzothiazolyl).

N-ethyl-2-benzothiazolecarboxamidine. /44/: (DMSO, d_6)

1.2 (t, 3H, $-CH_3$); 3.25 (q, 2H, CH_2); 6.65 (broad, 2H, NH_2);
7.45-8.0 (m, 4H, 2-benzothiazolyl).

N-Isopropyl-2-benzothiazolecarboxamidine. /46/: ($CDCl_3$)

1.32 (d, 6H, $C(CH_3)_2$); 3.75 (m, 1H, CH); 5.53 (very broad, 2H, NH_2);
7.44-8.0 (m, 4H, 2-benzothiazolyl).

N-Benzyl-2-benzothiazolecarboxamidine. /47/: (DMSO, d_6)

4.43 (s, 2H, CH_2); 6.84 (broad, 2H, NH_2); 7.35-8.02 (m, 9H, phenyl
and 2-benzothiazolyl).

N-(2-Phenethyl)-2-benzothiazolecarboxamidine. /48/: (DMSO, d_6)

2.9 (t, 2H, $-CH_2-$); 3.4 (t, 2H, $=N-CH_2$); 6.65 (broad, s, 2H, NH_2)
7.27-7.95 (m, 9H, phenyl and 2-benzothiazolyl).

N-2(3-Phenpropyl)-2-benzothiazolecarboxamidine. /50/: (DMSO, d_6)

1.09 (d, 3H, $-CH_3$); 2.76 (t, 2H, CH_2); 3.82 (m, 1H, CH);
6.52 (broad, 2H, NH_2); 7.15, 7.46 -7.96 (m, 9H, phenyl and 2-benzo-
thiazolyl).

N-p-tolyl-2-benzothiazolecarboxamidine. /52/: (DMSO, d_6)

2.33 (s, 3H, CH_3); 6.69 (s, 2H, NH_2); 7.08 (q, 4H, );
7.56-8.13 (m, 4H, 2-benzothiazolyl).

When optically active primary amines were used as starting material, the amidines obtained were also optically active, showing that the reaction took place with retention of configuration : Specific Rotation of N-(1-Phenethyl)-2-benzothiazolecarboxamidine /49/ : $[\alpha]_D^{24} = +324^\circ$ (c= 1 % chloroform solution); Specific Rotation of N-2(3-phenpropyl)-2-benzothiazolecarboxamidine /50/ : $[\alpha]_D^{25} = +118.5^\circ$ (c= 1 % chloroform solution).

EXPERIMENTAL

Melting points (mp) are uncorrected and were carried out on Kofler block.

Elemental microanalyses were performed by Dr. Kurt Eder in the ' Laboratoire de microchimie ' of the University of Geneva.

Spectral Analysis : (143, 144, 145)

The infra-red (ir) spectra were recorded on a Perkin-Elmer Grating Spectrophotometer, Model 257. The spectra described by their major and characteristic absorption bands were obtained as nujol mulls and/or KBr disks. The ir solution spectra were carried out in previously AR dried solvents as CCl_4 , CHCl_3 or as indicated. Usually 1 to 2 % solutions with 0.01 mm thickness Perkin-Elmer cells were used. The relative intensity and shape of the peaks are also described. Band characteristics and relative intensities: s= strong; m= medium; w= weak; v= very; sh= shoulder; b= broad.

Scale of relative intensities in percentage transmission :

vw, >85; m, 30-70; w, 70-85; s <30.

The ultraviolet (uv) spectra were recorded on either Perkin-Elmer, Model 402 spectrophotometer or Beckmann DU spectrophotometer.

The mass spectra were recorded on the MAT ATLAS CH 4 spectrometer.

The specific rotations were determined with Perkin-Elmer Model 401, Polarimeter.

Nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer spectrometer, Model R-12, at normal temperature (ca.30) with tetramethylsilane as an internal standard. The data are given in δ ppm.

SYNTHESIS

Starting Material:

Cyano-ethyl formate. /1/

It was synthesized by the method of Wallach (51) and Ulpian (52). 11.7 g (0.1 mole) of oxamide ethyl ester were mixed thoroughly with the equivalent amount 14.2 g (0.1 mole) of powdered phosphorus pentoxide, in a distillation flask surmounted by a distillation equipment. The reaction mixture was heated in an oil-bath. When the temperature of the oil-bath reached 120°, a clear liquid separated from the white solids. The cyano-ethyl formate started distilling at 111-112°. On the whole three different fractions were collected, which showed the same physical and spectroscopic characteristics. The distilled product weighed 5.68 g (57.4 % yield). The product was characterized by its infrared spectrum:

ν (C $\equiv$ N), 2250 cm^{-1} ; ν (C=O), 1754 cm^{-1} ; ν (C-O), 1252 cm^{-1} .

Benzothiazole-2-carboxamide. /2/.

One of the earliest and most valuable methods for the synthesis of benzothiazole is the reaction of O-amino-thiophenol with carboxylic acid (53) or its derivatives (74, 55). The following procedure describes the preparation of carboxamide in an one-step process instead of the three-steps reaction already described (56, 57, 58). The simplicity of the procedure and the purity of the resulting product, along with the common starting materials make this synthesis an interesting one.

9.09 g (0.1 mole of cyano-ethyl formate were added drop-wise to a well stirred solution of O-aminothiophenol 12.5 g (0.1 mole) in 100 ml methanol at 0° to 5° during one hour. After the

addition the reaction mixture was kept at room temperature. Within 3 hrs. benzothiazole-2-carboxamide started precipitating. After standing for 24 hrs., the precipitated solids were filtered, sucked thoroughly at vacuum, washed with dry ether to give 9.7 g (55 % yield) of carboxamide. Recrystallization from glacial acetic acid and little water gave an analytically pure product, mp: 228-230° (lit.(59) mp: 228-230°).

Analysis : Calculated for $C_8H_6N_2OS$ (178.21)

Cal. : N 15.73 %

Found : N 15.61 %

Infrared : ν (N-H): 3330(m), 3270(m), 3225(m), 3180(m) cm^{-1} (bonded NH)
 ν (C=O): 1695(m), 1665(s), cm^{-1} , (amide I); δ (N-H): 1620(m) cm^{-1}
 (amide II) ; δ (C-H): 1510(m), 755(m), 728(m), cm^{-1} , (benzothiazole).

Benzothiazole-2-carboxylic acid. /3/.

It was prepared as per the procedure described by Gilman and Beel (60). The yields upto 55 % were obtained. mp: 104-105° (with CO_2 evolution), (lit.(60) mp: 105°; (59) mp: 108°)

Infrared : ν (OH): 2630, 2480, (m), cm^{-1} , (bonded); ν (C=O): 1710 (m) cm^{-1}
 ν (C-O): 1273(s) cm^{-1} ; δ (C-H): 1502(s), 756(s), 722(s), cm^{-1} , (benzothiazole)

Benzothiazole-2-carbonyl chloride. /4/

This acid chloride was prepared by the modified procedure of Fridman (61). 90 g(0.5 mole) of benzothiazole-2-carboxylic acid were dissolved in about 1 litre of dry ether. Added to it 104 g (0.5 mole) of phosphorus pentachloride. The reaction mixture was stirred vigorously at low temperature (ca. 5-10) for 8 hrs. The disappearance of the phosphorus pentachloride from the reaction mixture indicated completion of the reaction. On evaporation of the solvent in vacuo, it gave the acid chloride as yellow-brown solids.

Without further purification it was used in the synthesis of benzothiazole-2-carboxamide.

Benzothiazole-2-carboxamide (/2/) from benzothiazole-2-carbonyl chloride.

(a) To a well-cooled (800ml) solution of ammonium hydroxide (ca 12.5 %) was added slowly benzothiazole-2-carbonyl chloride (ca 99g), with continuous stirring. After the addition of acid chloride was completed (ca 2 hrs), the whole reaction mixture was kept standing at room temperature for overnight. Carboxamide formed was filtered and washed with cold water to give 76g (84 % yield). It was purified as described before.

(b) In a solution of benzothiazole-2-carbonyl chloride (20g) in chloroform (200ml), cooled in ice-salt bath, passed a slow stream of dry ammonia gas till saturation. After standing at room temperature overnight, part of the solvent (ca 100ml) was evaporated in vacuo. The precipitated white solids filtered and washed with ether weighed 11.6g (67 % yield), mp 220-228°. Mother liquor contained unreacted acid chloride.

Benzothiazole-2-carbonitrile (2-cyano-benzothiazole) /5/

62.0g (0.346 mole) of benzothiazole-2-carboxamide were suspended in 1050 ml of alcohol free from chloroform (62) and added to it 90 ml of phosphorus-oxychloride (63). The reaction mixture was refluxed with calcium chloride guard tube for 20 hrs. After cooling to room temperature 500ml of ice cold water were added to dissolve inorganic impurities. The chloroform layer separated and extracted several times with 5% cold sodium bicarbonate solution, till free from acid. The chloroform layer was washed two more times with ice cold water and dried over anhydrous sodium sulphate. The

chloroform was evaporated at reduced pressure to give 2-cyano benzo-thiazole weighing 54.6 g (98.1 % yield). This crude product was purified by sublimation at 60-70° in high vacuo. Seven different crops giving a total of 46.58g (83.6 % yield) were collected. It was sufficiently pure to be used for condensation reactions. The different fractions had different melting points varying between 74-80°; but the recrystallized product from ether-petroleum ether mixture gave mp 78-80° (lit. (56) mp: 78-80° chloroform-isooctane). The product was characterized by its infrared spectrum.

Analysis : Calculated for $C_8H_4N_2S$ (160.20)

Cal : C 59.96 ; H 2.51 ; N 17.48 ; S 20.01 %

Found : C 60.17 ; H 2.52 ; N 17.59 ; S 20.06 %

Infrared : (nujol mull)

$\nu(C\equiv N)$ 2218m, cm^{-1} ; $\nu(C=N)$ 1630vw, cm^{-1} ; $\delta(C-H)$ 765s, 730m, cm^{-1} .

O-Methyl-2-benzothiazole-2-carboximidate /6/

The general methods for the preparation of imidates have been discussed (33). The following simple method has been used with success.

2-cyano-benzothiazole (1.0g) dissolved in about 30 ml of methanol and passed dry ammonia gas in the reaction mixture till saturation of the ammonia (ca 5-10 min.). This warm solution was kept for 15 minutes at room temperature. The solvent was evaporated in vacuo to give white crystalline product (1.2 g). Recrystallization from minimum quantity of methanol gave an analytically pure product mp : 90-92°.

Analysis : Calculated for $C_9H_8N_2OS$ (192.24)

Cal. : C 56.25 ; H 4.16 ; N 14.58 ; S 16.66 %

Found : C 56.18 ; H 4.13 ; N 14.56 ; S 16.80 %

Infrared: (nujol mull)

ν (=NH) 3297w cm^{-1} ; ν (C=N) 1643s cm^{-1} .

NMR : δ ppm; CH_3SOCH_3 (d_6)

3.91 (s with m): OCH_3 ; 9.22(s) : C=NH ; 7.46-8.03 (m): benzothiazole, (4 protons).

O-Methyl-benzothiazole-2-carboximide, monohydrochloride

It was synthesized by the Pinner synthesis using ether as a diluent (65,31,67,68).

To a solution of 4.8g (30 mmole) of 2-cyano-benzothiazole in 50 ml methanol was passed dry hydrochloric acid gas at 0° till saturation of methanol. The reaction mixture was diluted with 100 ml of dry ether and kept at -15° for overnight; whereby crystallization of the monohydrochloride of carboximide occurred. It was filtered and washed with dry ether and was used immediately without any further purification

Syn (NH_2) -(OH) (OC_2H_5) Amidines. (Z Isomers)

(Enolic Amidino Acid Esters)

N-(1-Benzyl-2-ethoxy-2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamide

/7/

0.48g (3 mmole) of 2-cyano-benzothiazole was dissolved in 15 ml of methanol. Added to it 0.687 g (3 mmole) of L-phenylalanine ethyl ester hydrochloride. The hydrochloride was neutralized by adding 0.3 g (3 mmole) of triethylamine. The solution was then refluxed for 22 hrs.. On cooling an intense yellow coloured product crystallized; it was filtered and washed with cold methanol to give

0.762 g (72.3 % yield) of the product. By recrystallization from boiling methanol, an analytically pure product was obtained.

Analysis : Calculated for $C_{19}H_{19}N_3O_2S$ (353.45)

Cal. : C 64.58 ; H 5.38 ; N 11.89 ; S 9.06 %

Found : C 64.46 ; H 5.32 ; N 11.96 ; S 9.21 %

Ultraviolet : (methanol)

λ max. 349 m μ (ϵ 13250)

227 m μ (ϵ 13950)

Infrared : see TABLE 1

N-(2-ethoxy-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarbox-
amidine. /8/

To a solution of 0.8g (5 mmole) of 2-cyano-benzothiazole in 20 ml of methanol, were added 0.97 g (5 mmole) of DL-leucine ethyl ester hydrochloride and 0.506 g (5 mmole) of triethylamine. The solution was refluxed for 12 hrs.. On cooling the solvent was evaporated in vacuo. The yellow solid obtained was then triturated with water (ca. 50 ml), filtered and washed 3 times with sufficient water. Vacuum dried product weighed 1.28 g (80.5 % yield). An analytical sample was prepared by recrystallization from ethanol

Analysis : Calculated for $C_{16}H_{21}N_3O_2S$ (319.43)

Cal. : C 60.18 ; H 6.58 ; N 13.16 ; S 10.03 %

Found : C 60.71 ; H 6.01 ; N 13.29 ; S 9.99 %

Ultraviolet : (methanol)

λ max. 360 m μ (ϵ 16130)

225 m μ (ϵ 12280)

Infrared : see TABLE 1

N-(2-Ethoxy-2-hydroxy-1-methylvinyl)-(Z)-2-benzothiazolecarbox -
amidine. /9/

A solution of 2-cyano-benzothiazole 1.2g(7.5 mmole) DI-alanine ethyl ester hydrochloride 1.15 g (7.5 mmole) and triethylamine 0.75 g (7.5 mmole), in 25 ml of methanol was refluxed for 9 hrs.. Part (ca. 15 ml) of the solvent was then evaporated in vacuo; On cooling the yellow product which crystallized was filtered and washed three times with 10 ml portions of cold methanol. After thorough drying in a high vacuo the weight of the product was 0.789 g (46 % yield). An analytical sample was tried to be prepared by recrystallizations from ethanol but the product was always slightly contaminated with the corresponding 5(4)-imidazolone derivative. Attempted recrystallizations in the similar fashion showed little higher carbon content than the theoretical value.

Analysis : Calculated for $C_{13}H_{15}N_3O_2S$ (277.35)

Cal. : C 56.31 ; H 5.41 ; N 15.16 %

Found : C 58.14 ; H 5.20 ; N 15.19 %

Infrared : see TABLE 1

Syn (NH₂)-(OH) (OH) Amidines . (Z Isomers)

(Enolic Amidino Acids)

N-(1-Benzyl-2,2-dihydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine,
monohydrobromide. /10/

N-(Amino-2-benzothiazolylmethylene)-3-phenyl-t-butyl ester, (E)-L-alanine, 0.5 g (1.3 mmole) were dissolved in 59 ml of 10 % hydrobromic acid in glacial acetic acid. The reaction solution was kept standing at room temperature for 20 hrs.. The precipitated intense yellow product was filtered and washed copiously with dry

ether to give 0.423 g of the product (84 % yield). An analytical sample prepared by three repeated recrystallizations from methanol-ether mixture, gave a yellow crystalline product, mp 202-204°.

This compound showed no optical activity. When hydrolyzed in presence of 6N HCl at 100° for 15 hrs it yielded DL-phenylalanine; this was confirmed by comparison with an authentic sample.

Analysis : Calculated for $C_{17}H_{16}BrN_3O_2S$ (406.32)

Cal. : C 50.24 ; H 3.94 ; Br 19.70 ; N 10.34 ; S 7.88 %

Found : C 50.44 ; H 4.07 ; Br 19.75 ; N 10.22 ; S 7.84 %

Ultraviolet : (methanol)

λ max. 354 m μ (ϵ 46720) ;

210 m μ (ϵ 41440) .

Infrared : see TABLE 2

NMR : δ ppm , CH_3OH (d_4)

4.07 (s, 2H, $-CH_2-$); 5.09 (s, 5H, NH_3^+ , 2(OH)); 7.25, 7.35-8.03

(s,m, 9H, phenyl and benzothiazole)

N-(1-Benzyl-2,2-dihydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine. /11/

To a solution, 0.2 g (0.49 mmole) of N-(1-benzyl-2,2-dihydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine, monohydrobromide /10/, in 1.5 ml of methanol was added 0.197 g (0.49 mmole) of triethylamine. The free base crystallizes, which was filtered and washed three times with cold methanol to give 0.14 g (87 % yield). The product was sufficiently pure and no further purification was necessary.

Analysis : Calculated for $C_{17}H_{15}N_3O_2S$ (325.39)

Cal : C 62.78 ; H 4.81 ; N 12.92 ; S 9.84 %

Found : C 62.95 ; H 4.66 ; N 12.86 ; S 9.66 %

Ultraviolet : (methanol) λ max. 357 m μ (ϵ 41320), 213 m μ (ϵ 46610)

Infrared : see TABLE 2

N-(2,2-dihydroxyvinyl-1-methyl)-(Z)-2-benzothiazolecarboxamidine, monohydrobromide. /12/

0.31 g (1 mmole) of N-(amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-L-alanine, dissolved in 20 ml of glacial acetic acid. Added to it 5 ml of 40 % hydrobromic acid in glacial acetic acid. The reaction mixture was allowed to stand at ambient temperature for 20 hrs. away from humidity. The resulting yellow crystalline product in the solution which was filtered and washed thoroughly with dry ether, weighed 0.269 g (80.7 % yield). Four repeated recrystallizations of this salt from methanol-ether mixture gave yellow crystals, mp 231-233°. Acid hydrolysis gave DL-alanine.

Analysis : Calculated for $C_{11}H_{12}BrN_3O_2S$ (330.22)

Cal : C 40.01 ; H 3.66 ; Br 24.20 ; N 12.72 ; S 9.71 %

Found : C 40.15 ; H 3.70 ; Br 24.34 ; N 12.62 ; S 9.60 %

Ultraviolet : (methanol)

λ max. 355 m μ (ϵ 22070), 214 m μ (ϵ 14640)

Infrared : see TABLE 2

N-(2-Bromo-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarboxamidine, monohydrobromide . /13/

0.521 g (1.5 mmole) of N-(amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-L-leucine, were dissolved in 40 ml of 10 % hydrobromic acid in glacial acetic acid, and kept at room temperature. After about 5 hrs. some yellow precipitation in the reaction flask was observed. The reaction was kept on further standing for 15 hrs. more. A golden yellow mass of precipitate, quickly filtered and washed copiously with dry ether and dried in high vacuo, gave 0.4 g (61.5 % yield). Attempted recrystallization

from common solvents mixtures like methanol-ether (ca. 1:10) afforded only oil; but on adding a large excess of ether the oil started crystallizing on trituration. It was recrystallized two more times in the similar fashion, mp. 236-238°.

Analysis : Calculated for $C_{14}H_{17}Br_2N_3OS$ (435.21)

Cal : C 38.62 ; H 3.90 ; Br 36.78 ; N 9.65 ; S 7.35 %

Found : C 38.73 ; H 4.10 ; Br 36.71 ; N 9.59 ; S 7.35 %

Ultraviolet : (methanol)

λ max. 354 m μ (ϵ 22830)

208.5 m μ (ϵ 17080)

Infrared : see TABLE 2

Anti (NH₂) Amidines. (E Isomers)

Three different procedures have been used to synthesize anti-(NH₂) amidines, by the reaction between benzothiazole-2-carboximidate and α -amino acid esters as the free bases.

Procedure I

Acid-catalysed condensation at room temperature with methanol-ether mixture as a solvent:

Equimolar quantities of carboximidate hydrochloride and α -amino acid ester were dissolved in a methanol-ether (ca. 1:5) mixture. The reaction takes place at room temperature, while the reaction time depends on the quantity of methanol in the mixture of solvents and also on the reactivity of the amino component. Two of the anti-(NH₂) amidines (E Isomers) with L-phenylalanine ethyl ester and DL-leucine ethyl ester derivatives have been prepared by this procedure.

Procedure II

At reflux temperature of methanol :

Benzothiazole-2-carbonitrile and α -amino acid ester hydrochloride(equimolar quantities) were dissolved in methanol. The hydrochloride was neutralized with an equivalent amount of triethylamine and the mixture was refluxed for 3 to 20 hrs. depending on the reactivity of the amino constituent. After evaporation of the solvent the solid was triturated with water to remove triethylamine hydrochloride, leaving the reaction product which was filtered and washed with more water. Yields upto 80-90 % were obtained in different cases. Glycine ethyl ester derivative was synthesized by this method. Also anti-(NH₂) amidines having t-butyl ester substituents in the cases of five α -amino acids were synthesized namely: L-phenylalanine, L-alanine, L-leucine, L-valine and glycine.

Procedure III

Without acid catalyst at room temperature with methanol-ether as a solvent :

Benzothiazole-2-carboximidate and α -amino acid ethyl ester dissolved in a methanol-ether (ca. 1:5) mixture as a solvent gave anti-(NH₂) amidines after standing at room temperature for 20 to 75 hrs.. The condensed products of phenylglycine ethyl ester, valine ethyl ester and diethyl malonate derivatives were successfully carried out.

N-(Amino-2-benzothiazolylmethylene)-3-phenyl-ethyl ester, (E)-L-alanine. /14/

1.71 g (7.5 mmole) of methyl-benzothiazole-2-carboximidate hydrochloride were dissolved in 30 ml of methanol and diluted with 100 ml of dry ether. To this solution was added 1.36 g (7.5 mmole) of L-phenylalanine ethyl ester. The reaction mixture

was kept at room temperature for two days. The solvent was evaporated to have 2.51 g (95 % yield), mp 132-138°, of the salt of amidine as an off-white solid. Three repeated recrystallizations from boiling methanol gave analytically pure product as a free amidine, (with the liberation of free HCl), mp 138-140°.

Analysis : Calculated for $C_{19}H_{19}N_3O_2S$ (353.45)

Cal. : C 64.55 ; H 5.41 ; N 11.88 ; S 9.07 %

Found : C 64.70 ; H 5.46 ; N 11.80 ; S 9.20 %

Ultraviolet : (methanol)

Specific rotation :

λ max. 207.5 m μ (ϵ 30980)

$[\alpha]_D^{24} = -142.5^\circ$

280 m μ (ϵ 16900)

(2 % chloroform)

Infrared : see TABLE 3 & 4

NMR : δ ppm, $CHCl_3$ (d)

1.18 (m, 3H, $-CH_3$); 3.21 (d and s, 2H, $-CH_2-C_6H_5$); 4.09 (m, 3H, $-COOCH_2$ and $CH-C_6H_5$); 5.61 (b, 2H, NH_2); 7.19 and 7.39-7.78 (m, 9H, phenyl and benzothiazole)

N-(Amino-2-benzothiazolylmethylene)-ethyl ester, (E)-DL-leucine, monohydrochloride. /15/

To a solution of 1.92 g (10 mmole) of methyl-benzothiazole-2-carboximide in 30 ml methanol was added 3N HCl in methanol (10 mmole). To this mixture was added 100 ml ethereal solution of DL-leucine ethyl ester and the whole reaction mixture was kept at room temperature for two complete days. The evaporation of the solvent gave an oil, which was tried to be crystallized in different common solvents; but with no success. The oil crystallized at the end in acetone-ether mixture at -30°, after two days standing to give 0.9 g (25 % yield) of the amidine monohydrochloride. An analytical sample was obtained by three recrystallizations from methanol-ether mixtures mp 122-125°.

Analysis : Calculated for $C_{16}H_{22}ClN_3O_2S$ (355.88)

Cal. : C 54.01 ; H 6.23 ; Cl 9.96 ; N 11.81 ; S 9.01 %

Found : C 53.98 ; H 6.10 ; Cl 10.03 ; N 11.87 ; S 9.00 %

Infrared : $\nu(NH_2^+)$: 3418 m, 3313 m; $\nu(C=O)$: 1724 m; $\nu_{as}(N=C-N)^+$: 1695 m, sh, 1630 m; $\delta(NH_3^+)$: 1568 m, b; $\nu(C-O)$: 1208 m; $\delta(C-H)$: 762 m, 735 m, 717 m, cm^{-1} .

N-(Amino-2-benzothiazolylmethylene)-ethyl ester, (E)-DL-leucine. /15A/

Isolation of this free amidine has been achieved by dissolving 0.2 g (0.57 mmole) of amidine monohydrochloride /15/ in 1 ml methanol. To this solution was added triethylamine 0.057 g (0.57 mmole) and the reaction mixture was diluted with water till complete precipitation of the free base, amidine. The precipitates were collected and washed with water. Three recrystallizations from a mixture of methanol-water yielded the pure amidine as off-white crystals, mp 78-80°.

Analysis : Calculated for $C_{16}H_{21}N_3O_2S$ (319.43)

Cal. : C 60.16 ; H 6.62 ; N 13.15 ; S 10.03 %

Found : C 60.20 ; H 6.59 ; N 13.05 ; S 10.15 %

Ultraviolet : (methanol)

λ_{max} . 207.5 m μ (ϵ 22350)

280 m μ (ϵ 16350)

Infrared : see TABLE 3

N-(Amino-2-benzothiazolylmethylene)-ethyl ester, (E)-glycine. /16/

0.8 g (5 mmole) of benzothiazole-2-carbonitrile was dissolved in 40 ml of methanol. Added to this solution 0.697 g (5 mmole) of glycine ethyl ester hydrochloride and 0.48g (5 mmole) of triethylamine. The colouration of the reaction mixture changed from yellow to dark green. After three hours at ambient temperature the solvent was evaporated at reduced pressure and the reaction product was extracted in dry ether to give 0.89 g (68.5 % yield)

The grey solid was washed three times with little quantity of ether, yielding an analytically pure product, mp 114-118°, without any further recrystallization.

The same experiment was carried out with no other change than the reaction temperature which was raised for 10 to 15 minutes to the boiling temperature of methanol; the same final product was obtained.

Analysis : Calculated for $C_{12}H_{13}N_3O_2S$ (263.32)

Cal. : C 54.75 ; H 4.94 ; N 15.97 ; S 12.12 %

Found : C 54.70 ; H 4.97 ; N 16.13 ; S 12.08 %

Ultraviolet : (methanol)

λ max. 227 m μ (ϵ 12480)

277 m μ (ϵ 13060)

Mass spectra : M^+ = 263

Infrared : see TABLE 3

N-(Amino-2-benzothiazolylmethylene)-ethyl ester, (E)-DL-valine. /17/

Methyl-benzothiazole-2-carboximide 1.92 g (10 mmole) and DL-valine ethyl ester 1.81 g (10 mmole) were dissolved in 150 ml of dry ether and 5 ml of methanol and the reaction mixture was kept at room temperature for four days. The solvent was evaporated at reduced pressure, the residue was triturated with little ether (ca. 30ml) and the precipitated solids filtered. The second crop was isolated in the similar fashion from the mother liquor to have the total of 1.40 g (45 % yield) of the amidine. After two recrystallizations from a mixture of ether-petroleum ether, an analytical sample was obtained, mp 72-74°.

Analysis : Calculated for $C_{15}H_{19}N_3O_2S$ (305.40)

Cal. : C 58.99 ; H 6.27 ; N 13.76 ; S 10.49 %

Found : C 59.18 ; H 6.26 ; N 13.83 ; S 10.60 %

Infrared : see TABLE 3

N-(Amino-2-benzothiazolylmethylene)-3-phenyl-ethyl ester, (E)-glycine. /18/

0.96 g (5 mmole) of methyl-benzothiazole-2-carboximidate and 1.07 g (5 mmole) of DL-phenylglycine ethyl ester hydrochloride were dissolved in 25 ml of methanol. To this solution were added 0.505 g (5 mmole) of triethylamine and 50 ml of dry ether. The colour of the solution changed to yellow. After 2 hrs. standing at room temperature the solvent was evaporated at vacuo to give pale yellow coloured solids weighing 1.48 g (87.8 % Yield). The analytically pure sample was prepared by two recrystallizations from methanol at reflux, mp 132-133°.

Analysis : Calculated for $C_{18}H_{17}N_3O_2S$ (339.42)

Cal. : C 63.70 ; H 5.04 ; N 12.38 ; S 9.44 %

Found : C 64.00 ; H 5.13 ; N 12.35 ; S 9.50 %

Infrared : see TABLE 3 & 4

NMR : δ ppm, CD_3SOCD_3

1.15 (t, 3H, $-CH_3$); 4.12 (m, 3H, $COO-CH_2-$ and $CH-COO-$); 5.54 (s, 2H, $-NH_2$); 7.0 (s, 5H, phenyl); 7.48-8.08 (m, 4H, benzothiazole)

N-(Amino-2-benzothiazolylmethylene)-3-carbethoxy-ethyl ester, (E)-malonate. /19/

Ethyl malonate from its hydrochloride :

1.057 g (5 mmole) of ethyl-amino-malonate hydrochloride were dissolved in 20 ml of methanol and added to it 0.505 g (5 mmole) of triethylamine and the solvent was evaporated at reduced pressure. The ethyl-amino-malonate was extracted with dry ether (ca. 40 ml).

Condensation :

To the ethereal solution (40 ml, see above) of ethyl-amino-malonate were added 0.96 g (5 mmole) of methyl-benzothiazole

-2-carboximide and 8 ml of methanol. The reaction solution was kept at room temperature for 24 hrs.. The evaporation of the solvent in vacuo gave pale yellow liquid, which crystallized by scratching on the walls of the reaction flask in the presence of little ether. The crystalline product was collected at vacuum and washed repeatedly with small portions of ether. Further, two more crops were collected from the mother-liquor in the similar fashion to give 1.05 g (84.4 % yield) of the amidine derivative. The pure product mp 98-99°, was obtained by recrystallization from a mixture of dioxane-petroleum ether. The compound was characterized by its infrared spectrum.

Analysis : Calculated for $C_{15}H_{17}N_3O_2S$ (335.39)

Cal. : C 53.71 ; H 5.10 ; N 12.52 ; S 9.56 %

Found : C 53.65 ; H 5.08 ; N 12.72 ; S 9.45 %

Infrared : see TABLE 3

N-(Amino-2-benzothiazolylmethylene)-3-phenyl-t-butyl ester, (E)-L-alanine. /20/

It was synthesized by two different reaction conditions :

(a) 0.32 g (2 mmole) of 2-cyano-benzothiazole, 0.515 g (2 mmole) L-phenylalanine t-butyl ester hydrochloride were dissolved in 10 of dry methanol. To this mixture was added 0.202 g (2 mmole) of triethylamine and the reaction solution was refluxed for 6 hrs.. The solvent was evaporated in vacuo. Two different crops of the product were isolated using very little amount of methanol to have 0.649 g (85.5 % yield). An analytically pure product, mp 148-149° was prepared by two recrystallizations from boiling methanol.

(b) Methyl benzothiazole-2-carboximide 0.38 g (2 mmole) was dissolved in 30 ml of methanol and added to it HCl in methanol (2 mmole) and L-phenylalanine t-butyl ester in 100 ml of dry ether. The reaction mixture was kept at room temperature for 22 hrs.

0.724 g (87 % yield) of amidinium chloride was neutralized by dissolution in methanol in the presence of an equivalent amount of triethylamine. The free base was recrystallized as described above in (a).

Analysis : Calculated for $C_{21}H_{23}N_3O_2S$ (381.50)

Cal. : C 66.14 ; H 6.03 ; N 11.02 ; S 8.39 %

Found : C 66.18 ; H 6.07 ; N 11.12 ; S 8.33 %.....(a)

: C 66.25 ; H 6.12 ; N 11.06 ; S 8.40 %.....(b)

Infrared : SEE TABLE 3

NMR : δ ppm, CD_3SOCD_3

1.32 (s, 9H, $-C(CH_3)_3$) ; 3.04 (d, 2H, $-CH_2-$) ; 4.62 (t, 1H, $-CH-$) ;
6.70 (s,b, 2H, $-NH_2$) ; 7.19 and 7.28-7.96 (m, 9H, phenyl, benzothiazole).

Specific rotation : $[\alpha]_D^{25} = -84.75^\circ$ (2 % chloroform)

N-(Amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-L-alanine. /21/

0.8 g (5 mmole) of 2-cyano-benzothiazole, 0.908 g (5 mmole) of L-alanine t-butyl ester hydrochloride were dissolved in 30 ml of methanol. The hydrochloride was neutralized by addition of 0.505 g (5 mmole) of triethylamine. The reaction mixture was refluxed for 16 hrs. and the solvent was removed in vacuo. The residual solid was triturated with 50 ml of water, filtered and washed with 3 portions of 20 ml water, to give 1.33 g (88.1% yield) of the amidine derivative. The analytically pure product mp $130-132^\circ$ was prepared by two recrystallizations from methanol.

Analysis : Calculated for $C_{15}H_{19}N_3O_2S$ (305.40)

Cal. : C 58.97 ; H 6.27 ; N 13.75 ; S 10.47 %

Found : C 59.40 ; H 5.72 ; N 13.97 ; S 10.70 % ... (1)

: C 59.41 ; H 6.07 ; N 13.63 ; S 9.85 % ... (2)

Infrared : SEE TABLE 3 & 4

N-(Amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-glycine. /22/

Benzothiazole-2-carbonitrile 0.8 g (5 mmole), glycine t-butyl ester hydrochloride 0.838 g (5 mmole) were dissolved in 40 ml of dry methanol. To this solution was added triethylamine 0.505 g (5 mmole) and the reaction mixture was refluxed for 2½ hrs., turning to dark brown colour. The solvent was evaporated in vacuo. The brown solids were treated with 50 ml of water and the insolubles filtered and washed with more water, weighing 1.16 g (80 % yield) after drying. The product was dissolved in hot methanol and treated with activated carbon. The colourless filtrate obtained from above gave white crystalline product on cooling, which was filtered and dried, mp 162-163°.

Analysis : Calculated for $C_{14}H_{17}N_3O_2S$ (291.38)

Cal. : C 57.71 ; H 5.88 ; N 14.42 ; S 11.00 %

Found : C 57.86 ; H 6.08 ; N 14.31 ; S 11.05 %

Infrared : SEE TABLE 3

NMR : δ ppm, $CDCl_3$

1.4 (s, 9H, $-C(CH_3)_3$); 4.04 (s, 2H, $-CH_2-$); 5.94 (s, b, 2H, $-NH_2$);

7.7-8.14 (m, 4H, benzothiazole).

N-(Amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-L-leucine. /23/

0.4 g (2.5 mmole) of 2-cyano benzothiazole, 0.559 g (2.5 mmole) of L-leucine t-butyl ester hydrochloride were dissolved in 20 ml of methanol. To this solution was added 0.253 g (2.5 mmole) of triethylamine and the reaction mixture was refluxed for 18 hrs.. The solvent was evaporated at reduced pressure and the residue was triturated with 30 ml water. The insoluble reaction product was filtered and washed with water. After drying in vacuo, 0.715 g (82.5 % yield) of anti-(NH_2) amidine was obtained. After two recrystallizations by dissolution in minimum quantity of hot methanol

an analytically pure product, mp 120-121°, was obtained.

Analysis : Calculated for $C_{18}H_{25}N_3O_2S$ (347.48)

Cal. : C 62.21 ; H 7.25 ; N 12.08 ; S 9.20 %

Found : C 62.18 ; H 7.31 ; N 12.18 ; S 9.15 %

Infrared : SEE TABLE 3 & 4

NMR : δ ppm, $CDCl_3$

0.92 (m, 6H, $-C(CH_3)_2$); 1.43 (s, 9H, $-COOC(CH_3)_3$); 1.78 (m, 2H, $-CH_2-$);
4.12 (s, b, 1H, $-CH(Me)_2$); 5.79 (s, b, 1H, $-CH-COO-$); 6.63 (s, b, 2H, $-NH_2$);
7.37- 7.90 (m, 4H, benzothiazole)

N-(Amino-2-benzothiazolylmethylene)-t-butyl ester, (E)-L-valine. /24/

0.72 g (4.5 mmole) of benzothiazole-2-carbonitrile,
0.943 g (4.5 mmole) of L-valine t-butyl ester hydrochloride were
dissolved in 30 ml of methanol. To this solution was added 0.45 g
(4.5 mmole) of triethylamine. The clear reaction solution was then
refluxed for 20 hrs., after which the solvent was removed at reduced
pressure. The residual solid was triturated with 50 ml of water,
filtered and washed with little more water. The vacuum dried product
weighed 1.12 g (74.6 % yield). The analytical sample was recrystallized
three times from methanol-water mixtures and once with ether-
-petroleum ether mixture, mp 107-109°.

Analysis : Calculated for $C_{17}H_{23}N_3O$ (333.46)

Cal. : C 61.23 ; H 6.95 ; N 12.60 ; S 9.61 %

Found : C 61.36 ; H 7.12 ; N 12.68 ; S 9.55 %

Infrared : SEE TABLE 3 & 4

NMR : δ ppm, $CDCl_3$

1.02 (d, 6H, $-C(CH_3)_2$); 1.47 (s, 9H, $-COOC(CH_3)_3$); 2.35 (m, 1H, $-CH(Me)_2$);
3.84 (m, 1H, $-CH-COO-$); 5.77 (s, b, 2H, $-NH_2$); 7.43-8.01 (m, 2H, benzoth-
iazole).

AMIDINO - ACIDS (IMINO FORM)
(Zwitterionic Derivatives)

Preparation of Lithium salt of α -amino acid

Equimolar amounts (ca. 30 mmole) of α -amino acid and lithium hydroxide (LiOH) dissolved in 70 ml of water. The solvent was evaporated in vacuo. The residual solid was then treated with methanol and ether and once again the solvent removed in vacuo, gave white crystalline product. The preparation of lithium salt of L-valine is illustrative.

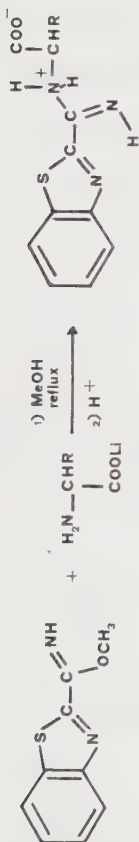
Lithium salt of L-valine :

3.51 g (30 mmole) of L-valine and 1.35 g (30 mmole) of lithium hydroxide (53 %) dissolved in 70 ml of water. The mixture was warmed and filtered to have a clear solution. The solvent was evaporated at reduced pressure and residual product was treated with methanol and ether (20 and 50 ml resp.). Once more the solvent was evaporated to dryness to yield white crystalline product, 3.62 g.

Synthesis of Amidino Acid (Imino Form)

Equimolar quantities of methyl benzothiazole-2-carboximidate and lithium salt of α -amino acid (ca. 10 mmole) were dissolved in 100 ml of methanol and the reaction mixture was refluxed for 1 to 24 hrs. depending on the reactivity of the α -amino acid derivative. The solution was cooled in an ice-salt bath and an equivalent amount (10 mmole) of 0.5N HCl was added. The solvent was evaporated in vacuo and the solids triturated with minimum quantity of cold water (ca. 40 ml). The undissolved solids filtered, washed carefully with cold water, dried and recrystallized. (see Table 9)
(FOR INFRA-RED SEE TABLE -6)

TABLE 9



Compd. No.	R	Hrs. Reflux	% Yield	Recry. Solvent	M.P. °C	Mol. For. (Mol. Wt.)	Analysis: Calculated: 1 Found: 2				
							C 1	H 1	N 1	S 1	S 2
/25/	-H	1	72.6	Washed with MeOH & ether	228-230	$\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2\text{S}$ (235.27)	51.05 50.97	3.85 3.80	17.86 17.80	13.62 13.50	
/26/	-CH ₃	21	57.8	MeOH + ether	167-170	$\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$ (249.29+ 18)	49.43 49.50	4.86 4.84	15.73 15.63	11.99 12.00	
/27/	-CH ₂ -C ₆ H ₅	24	74.1	Dioxane-light petrol.	179-181	$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (325.39)	62.74 62.58	4.64 4.69	12.91 12.74	9.85 9.70	
/28/	-CH(OH) ₃	18	67.3	MeOH + ether	168-170	$\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (277.35)	56.29 56.23	5.45 5.58	15.15 15.06	11.56 11.50	
/29/	-CH(OH) ₃ -CH ₂ -CH ₃	22	41.7	MeOH + ether + light petrol & DMF-ether	186-189	$\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ (291.38)	57.70 57.58	5.88 6.00	14.42 14.39	11.00 10.95	

2-(2-BENZOTHAZOLYL)-4-ALKYL(or ALKYLARYL)-2-IMIDAZOLIN-5-ONE.

General Procedure of 2-Imidazolin-5-one derivatives :

2-Imidazolin-5-one derivatives were prepared by sublimation of $\text{Syn}(\text{NH}_2)-(\text{OH})(\text{OC}_2\text{H}_5)$ amidines (Z isomers) in the high vacuum (ca. 0.05 mm) using an oil pump at the temperature of approximately 150° to 170° . The most of the fractions were obtained as an amorphous solid having intense yellow colour. The different fractions were characterized by their infrared spectra. On trituration of the different fractions in the presence of non-polar solvent, viz. ether, gave yellow crystalline product, as the pure analytical sample. The yields upto 80 % were obtained in the following three cases, (/30/,/31/,/32/).

2-(2-Benzothiazolyl)-4-benzyl-2-imidazolin-5-one. /30/.

It was obtained by sublimation of N-(1-benzyl-2-ethoxy-2-hydroxyvinyl)-(Z)-2-benzothiazolecarboxamidine,/7/, using aforementioned procedure.

Melting point: $184-186^\circ$.

Analysis : Calculated for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{OS}$ (307.38)

cal. : C 66.44 ; H 4.23 ; N 13.66 ; S 10.42 %

Found : C 66.62 ; H 4.33 ; N 13.81 ; S 10.22 %

Infrared : SEE TABLE 5

2-(2-Benzothiazolyl)-4-isobutyl-2-imidazolin-5-one. /31/.

It was obtained by sublimation of N-(2-ethoxy-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarboxamidine,/8/.

Melting point: $178-183^\circ$.

Analysis : Calculated for $C_{14}H_{15}N_3OS$ (273.36)

Cal. : C 61.53 ; H 5.49 ; N 15.38 ; S 11.72 %

Found : C 61.53 ; H 5.57 ; N 15.44 ; S 11.63 %

Infrared: SEE TABLE 5

2-(2-Benzothiazolyl)-4-methyl-2-imidazolin-5-one. /32/.

It was isolated by the sublimation of N-(2-ethoxy-2-hydroxy-1-methylvinyl)-(Z)-2-benzothiazolecarboxamidine, /9/.

Melting point: 207-210°

Analysis : Calculated for $C_{11}H_9N_3OS$ (231.28)

Cal. : C 57.14 ; H 3.89 ; N 18.18 ; S 13.85 %

Found : C 57.23 ; H 4.02 ; N 18.06 ; S 13.96 %

Infrared: SEE TABLE 5

Mass spectra: $M^+ = 231$

2-(2-Benzothiazolyl)-4-isopropyl-2-imidazolin-5-one. /33/

Equimolar quantities (5 mmole) of benzothiazole-2-carbonitrile, DL-valine ethyl ester hydrochloride and triethylamine were dissolved in 20 ml of methanol and refluxed the solution for 20 hrs.. The reaction mixture was cooled to room temperature and part of the solvent (ca. 10 ml) was removed at reduced pressure. The separated yellow crystalline product was filtered and washed with cold methanol, to give 0.6 g (40 % yield on the basis of open chain derivative). Attempted recrystallizations from ethanol to afford open chain product (syn(NH₂)-(OH)(OC₂H₅) amidine) failed. So part 0.150 g of the product was sublimed as per the general procedure already described, to give 0.110 g of 2-imidazolin-5-one derivative (73 % yield), mp 174-177°.

Analysis ; Calculated for $C_{13}H_{13}N_3OS$ (259.33)

Cal. : C 60.23 ; H 5.01 ; N 16.21 ; S 12.35 %

Found : C 60.28 ; H 5.13 ; N 16.27 ; S 12.42 %

Infrared : SEE TABLE 5

2-(2-BENZOTHAZOLYL)-2-IMIDAZOLE DERIVATIVES

2-(2-Benzothiazolyl)-4-carboethoxy-5-hydroxy-2-imidazole. /34/

An equimolar solution (10 mmole) of 2-cyano benzo-thiazole, ethyl-amino-malonate hydrochloride and triethylamine in 30 ml methanol was refluxed for 18 hrs. The reaction mixture was cooled to room temperature and part (ca. 15 ml) of the solvent was evaporated in vacuo. The resultant yellow precipitate was collected by filtration and washed with little quantity of cold methanol. The remaining mother liquor was concentrated at reduced pressure. The residual product was extracted with cold water and filtered to give totally 1.38 g (41.8 % yield) of 2-imidazole derivative. Two recrystallizations from methanol gave analytically pure product, mp 237-239°. The product gives intense blue colouration with ferric chloride solution. It was characterized by its infrared spectrum.

Analysis : Calculated for $C_{13}H_{11}N_3O_3S$ (289.32)

Cal. : C 53.97 ; H 3.80 ; N 14.53 ; S 11.07 %

Found : C 53.89 ; H 3.85 ; N 14.40 ; S 11.20 %

Infrared : SEE TABLE 5

2-(2-Benzothiazolyl)-4-carboethoxy-5-hydroxy-2-imidazole./35/.

To a solution of 1.6 g (10 mmole) of benzothiazole-2-carbonitrile in 25 ml of methanol, were added 2.39 g (10 mmole) of diethyl ester of glutamic acid hydrochloride and 1.01 g (10 mmole) of triethylamine. The solution was refluxed for 5 hrs.. Part of the

solvent (ca. 15 ml) was removed in vacuo. The pale yellow precipitated product was filtered and washed with minimum quantity of cold methanol. The mother liquor was concentrated and the residual product was treated with chloroform-water (1:1) mixture. The evaporation of chloroform after drying over anhydrous sodium sulphate, gave the second crop to afford the total of 1.74 g (48 % yield). An analytical sample was prepared by recrystallization from methanol, mp 203-205°.

Analysis : Calculated for $C_{15}H_{15}N_3O_3S$ (317.37)

Cal. : C 56.78 ; H 4.73 ; N 13.24 ; S 10.09 %

Found : C 56.80 ; H 5.02 ; N 13.35 ; S 10.25 %

Infrared : SEE TABLE 5

2-(2-Benzothiazolyl)-4-phenyl-5-hydroxy-2-imidazole. /36/.

Equimolar amounts (5 mmole) of 2-cyano benzothiazole, DL-phenylglycine ethyl ester hydrochloride and triethylamine in 30 ml of methanol as a solvent were refluxed for 16 hrs.. The reaction mixture was concentrated in vacuo to reduce half its volume. The precipitated intense yellow product was filtered and washed with minimum amount of methanol. Collected filtrates and washings were concentrated at the reduced pressure. To the residual product 30 ml of water were added and the precipitated yellow solid was filtered. The total yield of 1.35 g (92 % yield) was obtained. The purification was achieved by sublimation at 210° (0.01 mmHg) and trituration of the sublimed product several times with dry ether gave mp 245-248° (% yield of the sublimed product was 65%)

Analysis : Calculated for $C_{16}H_{11}N_3OS$ (293.35)

Cal. : C 65.51 ; H 3.77 ; N 14.32 ; S 10.93 %

Found : C 65.22 ; H 4.30 ; N 14.17 ; S 10.75 %

Infrared : SEE TABLE 5

2-(2-benzothiazolyl)-4-methyl-5-O-acetyl-2-imidazole. /37/.

0.2 g of N-(2-ethoxy-2-hydroxy-1-methylvinyl)-(Z)-2-benzothiazolecarboxamidine(/9/) were dissolved in 5 ml of glacial acetic acid. To this solution 5 ml of acetic anhydride was added and then the reaction mixture was allowed to stand at room temperature overnight. This solution was poured into 50 ml of ice water. The precipitated off-white product was filtered and washed with water, to give 0.17 g. After two recrystallizations from methanol an analytically pure product, mp 206-208°, was obtained.

Analysis : Calculated for $C_{13}H_{11}N_3O_2S$ (273.32)

Cal. : C 57.14 ; H 4.02 ; N 15.38 ; S 11.71 %

Found : C 57.01 ; H 4.17 ; N 15.52 ; S 11.67 %

Infrared : SEE TABLE 5

2-(2-Benzothiazolyl)-4-isobutyl-5-O-acetyl-2-imidazole. /38/.

The acetylation was carried out exactly as the procedure described above for /37/. 0.2 g of N-(2-ethoxy-2-hydroxy-1-isobutylvinyl)-(Z)-2-benzothiazolecarboxamidine,/8/, gave 0.15 g of O-acetyl imidazole derivative. Two repeated recrystallizations from methanol-water mixture gave analytically pure product, mp 163-164°.

Analysis : Calculated for $C_{16}H_{17}N_3O_2S$ (315.40)

Cal. : C 60.95 ; H 5.39 ; N 13.33 ; S 10.15 %

Found : C 60.96 ; H 5.48 ; N 13.56 ; S 10.27 %

Infrared : SEE TABLE 5

2-(2-Imidazolin-2-yl) benzothiazole. /39/.

To a solution of 1.6 g (10 mmole) of benzothiazole-2-carbonitrile in 20 ml of methanol were added 0.6 g (10 mmole) of ethylenediamine. The reaction mixture was allowed to stand at room temperature overnight. The evaporation of the solvent in vacuo gave 1.9 g (93 % yield) of the crude product. After four repeated recrystallizations from cyclohexane gave analytically pure product, mp 146-147° (lit.(135): mp 151-152°).

Analysis : Calculated for $C_{10}H_9N_3S$ (203.27)

Cal. : C 59.10 ; H 4.41 ; N 20.67 ; S 15.77 %

Found : C 59.32 ; H 4.40 ; N 20.69 ; S 15.70 %

Infrared : (nujol mull)

$\nu(N-H)$: 3282 m, b, cm^{-1} ; $\nu(N=C-N)$: 1610 m, 1590 m, cm^{-1} ;

$\delta(C-H)$: 1518 m, 761 m, 737 , 700 , cm^{-1} (benzothiazole)

NMR : δ ppm, $CDCl_3$

5.72 (s, very broad, 1H, -NH-); 6.17 (s, 4H, $-CH_2-CH_2-$);

7.38-7.91 (m, 4H, benzothiazole).

2-(1,4,5,6-tetrahydropyrimidin-2-yl) benzothiazole. /40/.

1.6 g (10 mmole) of benzothiazole-2-carbonitrile were dissolved in 30 ml methanol. To this solution were added 0.741 g (10 mmole) of 1,3-diaminopropane and the reaction mixture was refluxed for 20 hrs.. The solvent was concentrated in vacuo to give a pale yellow liquid, which on scratching the walls of the reaction flask in presence of little ether, was crystallized as a white solid. The precipitate was filtered and washed carefully with a very small amount of cold ether. The pure analytical sample was afforded by two recrystallizations from ether-petroleum ether, mp 129-130°, weight: 1.49 g (68.5 % yield)

Analysis : Calculated for $C_{11}H_{11}N_3S$ (217.29)

Cal. : C 60.80 ; H 5.10 ; N 19.33 ; S 14.75 %

Found : C 60.96 ; H 5.04 ; N 19.37 ; S 14.85 %

Infrared : (nujol mull)

ν (N-H): 3265 m, cm^{-1} ; ν (N=C-N): 1625 m, 1596 m, cm^{-1} ;

δ (C-H): 1529 m, 760 m, 731 m, cm^{-1} (benzothiazole).

2-(2-Benzoimidazolyl)-benzothiazole . /41/

0.43 g (3 mmole) of O-phenylenediamine mono-hydrochloride , 0.48 g (3 mmole) of benzothiazole-2-carbonitrile were mixed and heated at 200-210° in a sealed tube to a molten mass. The reaction was allowed to attain room temperature. The solidified orange product was taken in 20 ml of water and filtered. Once again the solid was triturated in 30 ml chloroform, the insoluble fraction represented the desired product, wt. 0.43 g (57.8 % yield). It was purified by sublimation at 180-220°, in the high vacuum, gave an analytical sample mp 288-289°.

Analysis : Calculated for $C_{14}H_9N_3S$ (251.31)

Cal. : C 66.93 ; H 3.58 ; N 16.73 ; S 12.75 %

Found : C 67.10 ; H 3.53 ; N 16.66 ; S 12.66 %

Infrared : (nujol mull)

ν (N-H): 3390 m, cm^{-1} ; ν (C=C) & (C=N): 1598 w, 1588 w, cm^{-1} ;

δ (N-H): 1550 m, cm^{-1} ; δ (C-H): 768 m, 750 m, 730 m, cm^{-1} .

N-ALKYL, N-ALKYLARYL and N-ARYL MONOSUBSTITUTED 2-BENZOTHAZOLE-CARBOXAMIDINES.

The reaction between N-alkyl, N-alkylaryl or N-aryl amines and benzothiazole-2-carbonitrile in methanol as a solvent at reflux gave respectively N-alkyl, N-alkylaryl or N-aryl monosubstituted 2-benzothiazolecarboxamidines.

GENERAL PROCEDURE :

Equimolar quantities of benzothiazole-2-carbonitrile and amine (ca. 10 mmole) were dissolved in 20 to 30 ml methanol and the reaction mixture was refluxed for 12 to 90 hrs. depending on the reactivity of the amino component. After evaporation of the solvent at reduced pressure and recrystallization from methanol as a solvent (or as indicated) gave about 80 % yield of N-monosubstituted 2-benzothiazolecarboxamidines. (see Table 10)

In certain cases wherein sulphate (/50/) or hydrochloride (/44/, /45/) salts have been used, they were neutralized with equivalent amount of triethylamine. When the reaction was over the solvent was evaporated in vacuo and the solid triturated with sufficient amount of cold water to remove the salt of triethylamine. The addition product was then recrystallized.

The amines having electronegative group like trifluoromethyl or sterically hindered amines as isopropylamine required relatively more reaction times. Optically active amino derivatives gave optically active monosubstituted amidines. N-aryl amidines are yellow coloured crystalline products while N-alkyl or N-alkylaryl amidines are white to off-white solids.

(FOR INFRA-RED SEE TABLE 7 & 8)

TABLE 10



Compd. No.	R	Hrs. Reflux	Yield %	Recry. solvent	M.P. °C	Mol. For. (Mol. Wt.)	Analysis: Calculated: Found: 2			
							C	H	N	S
/42/	-(CH ₂) ₃ -CH ₃	18	86	Ether + Pet. ether	63-65	C ₁₂ H ₁₅ N ₃ S (233.34)	61.77 61.78	6.48 6.28	18.01 17.95	13.74 13.60
/43/	-(CH ₂) ₂ -CH ₃	18	85	Ether + Pet. ether	73-74	C ₁₁ H ₁₃ N ₃ S (219.31)	60.24 60.12	5.97 5.98	19.16 19.20	14.62 14.60
/44/	-CH ₂ -CH ₃	18	83	MeOH + water	77-80	C ₁₀ H ₁₁ N ₃ S (205.28)	58.50 58.29	5.40 5.32	20.46 20.33	15.61 15.45
/45/	-CH ₃	18	52	MeOH + water	97-98	C ₉ H ₉ N ₃ S (191.26)	56.50 56.62	4.74 4.80	21.96 22.00	16.76 16.65
/46/	-CH(CH ₃) ₂	48	90	MeOH + water	98-98.5	C ₁₁ H ₁₃ N ₃ S (219.31)	60.24 60.24	5.97 6.08	19.16 19.08	14.61 14.40

Compd. No.	R	Hrs. Reflux	% Yield	Recry. solvent	M.P. °C	Mol.For. (Mol.Wt.)	Analysis: Calculated: Found %				
							C ₁	H ₁	N ₁	S ₁	
/47/	-CH ₂ -C ₆ H ₅	18	90	MeOH	113-114	C ₁₅ H ₁₃ N ₃ S (267.36)	67.40 67.54	4.90 4.82	15.72 15.58	11.99 11.95	
/48/	-CH ₂ -CH ₂ -C ₆ H ₅	20	83	MeOH + water	83-86	C ₁₆ H ₁₅ N ₃ S (281.38)	68.30 68.42	5.37 5.15	14.93 14.90	11.39 11.40	
/49/	-CH(CH ₃)-C ₆ H ₅	20	43	Ether (-86°)	88-89	C ₁₆ H ₁₅ N ₃ S (281.38)	68.30 68.45	5.37 5.23	14.93 14.98	11.39 11.48	
/50/	-CH(CH ₃)-CH ₂ -C ₆ H ₅	12	37	MeOH	113	C ₁₇ H ₁₇ N ₃ S (295.41)	69.15 69.40	5.76 5.89	14.23 14.24	10.84 10.72	
/51/	-C ₆ H ₅	18	85	MeOH	114-115	C ₁₄ H ₁₁ N ₃ S (253.33)	66.40 66.40	4.34 4.39	16.60 16.74	12.64 12.62	
/52/	-C ₆ H ₄ -CH ₃ -(p)	18	91	MeOH	135-136	C ₁₅ H ₁₃ N ₃ S (267.36)	67.41 67.35	4.86 4.99	15.73 15.74	11.98 12.05	
/53/	-C ₆ H ₄ -CF ₃ -(m)	90	65	MeOH	121-124	C ₁₅ H ₁₀ F ₃ N ₃ S (321.33)	56.07 56.31	3.13 3.33	13.07 12.98	9.98 10.05	F 17.74 17.60
/54/	-C ₇ H ₄ NS (-2-benzothiazolyl)	22	90	Dioxane	295	C ₁₅ H ₁₀ N ₄ S ₂ (310.41)	58.06 58.00	3.22 3.30	18.06 18.18	20.64 20.68	

2-Benzothiazolecarboxamidine /55/.

To a cooled solution of benzothiazole-2-carboximidate (0.96 g) in 20 ml of methanol, ammonia was passed till saturation of the solution. The reaction mixture was kept at room temperature in a well corked flask for 4 days. The solvent was removed at the reduced pressure to afford white product. By sublimation carboxamidine was purified from unreacted carboximidate, to give 0.4 g (44 % yield), mp 136-138° (lit. (55):mp 150°).

Analysis : Calculated for $C_8H_7N_3S$ (177.23)

cal. : C 54.23 ; H 3.95 ; N 23.72 ; S 18.07 %

Found : C 54.36 ; H 4.00 ; N 23.80 ; S 17.96 %

Infrared : (nujol mull)

ν_{NH_2} : 3478 m, $\nu_s(NH_2)$: 3295 w; $\nu_{as}(N=C-N)$: 1623 m, 1580 w, 1555 w ; $\delta(N-H)$: 1520 m ; $\delta(C-H)$: 765 m, 732 w, cm^{-1} .

2-Benzothiazolecarboxamidoxime. /56/.

0.8 g (5 mmole) of benzothiazole-2-carbonitrile, 0.347 g (5 mmole) hydroxylamine hydrochloride were dissolved in 20 ml of methanol. To this solution were added 0.5 g (5 mmole) triethylamine. Immediately white shining product started crystallizing in the reaction mixture, which was filtered and washed with little amount of cold methanol. The second crop was isolated from filtrate and washed to give a total amidoxime, 0.88 g (91.6 % yield). It was purified by two recrystallizations from methanol, mp 214-215°.

Analysis : Calculated for $C_8H_7N_3OS$ (193.23)

Cal. : C 49.74 ; H 3.62 ; N 21.76 ; S 16.58 %

Found : C 50.02 ; H 3.67 ; N 21.95 ; S 16.35 %

Infrared : (nujol mull)

$\nu(N-H)$: as 3500 m, s 3378 s, cm^{-1} ; $\nu(O-H)$: 3170 m, broad, cm^{-1} ;

$\nu_{as}(N=C-N)$ 1653 m, 1580 w, cm^{-1} ; $\delta(N-H)$: 1565 m, cm^{-1} ; (benzothiazole)

1524 w, cm^{-1} ; $\delta(C-H)$: 770 m, 762 m, 738 m, cm^{-1} .

N-(Imino-2-benzothiazolylmethyl)-2-benzothiazolecarboxamidine./57/.

0.8 g (5 mmole) of benzothiazole-2-carbonitrile were dissolved in 20 ml of t-butyl alcohol and 10 ml of ether. A slow stream of ammonia was passed into the reaction solution during 5 minutes. The reaction mixture was allowed to stand overnight at room temperature. The fluffy product crystallized in the reaction mixture, was filtered and washed with ether to give 0.56 g. Two recrystallizations from CHCl_3 gave pure product, mp 250-251°.

Analysis : Calculated for $\text{C}_{16}\text{H}_{11}\text{N}_5\text{S}_2$ (337.43)

Cal. : C 56.95 ; H 3.28 ; N 20.75 ; S 19.00 %

Found : C 57.30 ; H 3.32 ; N 20.47 ; S 19.10 %

Infrared : (Nujol mull): ν (N-H): 3328(w), 3278(w) cm^{-1} ;

ν_{as} (N=C-N): 1630(m), 1560(w) cm^{-1} ; δ (NH): 1529(m) cm^{-1} ;

δ (C-H) arom. : 751(m), 729(m), cm^{-1} .

Mass spectrum : $\text{M}^+ = 337$

AMIDINIUM CHLORIDE DERIVATIVES

General Procedure :

Benzothiazole-2-carboximidate (5 mmole) was dissolved in 30 ml methanol. To this solution an equivalent amount of HCl in methanol (5 mmole) and alkylaryl-amine (5 mmole) were added. The reaction mixture was allowed to stand at room temperature for 2 days. The solvent was evaporated in vacuo, the residual product was then recrystallized from methanol-ether mixture. The second recrystallization in the similar fashion gave analytically pure product. The following three amidinium chlorides, /58/, /59/, /60/, were prepared by this procedure. The yields upto 65 %, 75 %, 40 %, were obtained respectively, in these three cases.

N-Benzyl-2-benzothiazolecarboxamidine, monohydrochloride. /58/.

Melting point : 220-222 °

Analysis : Calculated for $C_{15}H_{14}ClN_3S$ (303.82)

Cal. : C 59.28 ; H 4.64 ; Cl 11.65 ; N 13.82 ; S 10.53 %

Found : C 59.23 ; H 4.76 ; Cl 11.75 ; N 13.73 ; S 10.50 %

Infrared : SEE TABLE 11

N-(2-Phenethyl)-2-benzothiazolecarboxamidine, monohydrochloride. /59/.

Melting point : 251-253 °

Analysis : Calculated for $C_{16}H_{16}ClN_3S$ (317.85)

Cal. : C 60.47 ; H 5.03 ; Cl 11.16 ; N 13.22 ; S 10.07 %

Found : C 60.53 ; H 5.13 ; Cl 11.17 ; N 13.07 ; S 10.10 %

Infrared : SEE TABLE 11

N-(1-Phenethyl)-2-benzothiazolecarboxamidine, monohydrochloride./60/.

Melting point : 220-222 °

Analysis : Calculated for $C_{16}H_{16}ClN_3S$ (317.85)

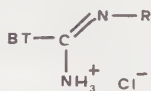
Cal. : C 60.47 ; H 5.07 ; Cl 11.16 ; N 13.22 ; S 10.07 %

found : C 60.30 ; H 5.00 ; Cl 11.20 ; N 13.10 ; S 10.00 %

Infrared: SEE TABLE 11

TABLE 11

Positions of absorption maxima (cm^{-1}) in the infra-red spectra of Amidinium Chloride Derivatives (KBr disks).



R	$\nu(\text{NH}_3^+)$	$\nu(\text{N}=\text{C}-\text{N})^+$	$\delta(\text{NH}_3^+)$	$\delta(\text{C}-\text{H})$ arom.
$-\text{CH}_2-\text{CH}_2\text{C}_6\text{H}_5$	3120 m	1686 m, 1632 m	1555 m	760 m 725 m 705 m
$-\text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$	3145 m, b	1670 m, 1618 m	1560 w	770 m 712 m
$-\text{CH}_2-\text{C}_6\text{H}_5$	3170 m, b	1673 m, 1625 m	1550 m	772 m 755 m 738 m 725 m 710 m

N-(Imino-2-benzothiazolylmethyl)-glycine, monohydrobromide /61/.

40 mg (0.138 mmole) of N-(Amino-2-benzothiazolyl-methylene-t-butyl ester, (E)-glycine, were dissolved in 3.5 ml of 15% hydrobromic acid in glacial acetic acid. After 5 minutes of reaction some pale yellow precipitate was seen. The reaction mixture was kept at room temperature for overnight. The crystallized product in the reaction mixture was then quickly collected by filtration, dissolved in methanol and reprecipitated with dry ether. Repeated two recrystallizations from methanol-ether mixtures gave a white analytically pure product, 23 mg (77.7 % yield), mp 210-215° (decomp.)

Analysis : Calculated for $C_{10}H_{10}BrN_3O_2S$ (316.196)

Cal. : C 37.98; H 3.18; Br 25.27; N 13.28; S 10.13 %

Found : C 37.90; H 3.32; Br 25.22; N 13.41; S 10.10 %

Ultraviolet : See Fig 12 and page

Infrared :

ν (NH): 3510w, 3428w, 3365m cm^{-1} ; ν (NH_3^+) 3110m cm^{-1}

ν (C=O): 1762 m; ν as (N=C-N)⁺ : 1668m, 1614 m cm^{-1}

δ (NH_3^+) : 1560 w cm^{-1} ; ν (C-O) 1200 m cm^{-1} ; δ (C-H) arom : 715 w 712w, sh; 698 m cm^{-1} .

NMR : CH_3OH (d_4)

4.47 (s, 2H, $-CH_2-$); 4.94 (s,b, 4H, NH_3^+ and COOH)

8.21-7.66 (m, 4H, 2-benzothiazolyl)

SUMMARY

The objective of the present work was the preparation and investigation of triadic systems in the particular case of 2-benzothiazolecarboxamidines obtained by condensation of benzothiazole-2-carbonitrile and primary amines. A serie of N-mono-substituted 2-benzothiazolecarboxamidine was then prepared.

The condensation of benzothiazole-2-carboximide with α -amino acid esters gives amidines with one possible tautomeric structure. Both syn- and anti- isomers of the single tautomer were characterized, demonstrating a geometrical isomerism around the imino group. The carboxylic esters and the free acids of syn-isomers exist exclusively as the enol form, whereas the anti-isomers prefer the carbonyl structure. The existence of these isomers was confirmed by ir, uv, and nmr spectroscopy.

When starting with optically active α -amino acid esters the anti- derivatives were obtained with retention of configuration while the syn- derivatives were optically inactive due to their enolized structure.

The configurational assignment was confirmed by the formation of cyclic derivatives in both cases.

a) Thermic cyclization:

When heated both anti- and syn- isomers yielded the same cyclic derivative. In the case of anti-isomers an intermediate on the way of cyclization has been proposed and could be synthesized.

b) Acid catalysed isomerization:

By the action of hydrobromic acid optically active anti-amino amidines (t-butyl ester substituents), (E Isomers), gave syn-amino enolized acid derivatives (Z Isomers) with no optical activity, resulting from their planar structure. The possibility to isolate these syn-amino enolized acid derivatives can be considered as an additional argument in favour of the existence of a planar intermediate in the mechanism leading to racemization of compounds exhibiting a prototropic change. Acid hydrolysis of these syn-derivatives afforded racemic α -amino acids.

Amidino acids (Imino form) were obtained by the action of lithium salt of α -amino acids on benzothiazole-2-carboximide. When heated these amidino acids (Imino form) yielded the corresponding 4(5H)-imidazolones, identical with those obtained from syn- and anti-isomers. The action of hydrobromic acid led to the same syn-isomer than that resulting from the acid isomerization of anti-amino isomers (t-butyl ester substituents).

The infra-red examination performed on solutions of these N-monosubstituted 2-benzothiazolecarboxamidines showed the preponderance of the amino form in the equilibrium mixture.

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